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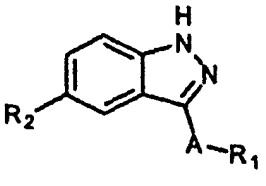
(54) Title: INDAZOLE DERIVATIVES AS JNK INHIBITORS AND COMPOSITIONS AND METHODS RELATED THERETO



(I)

(57) Abstract: Compounds having activity as selective inhibitors of JNK are disclosed. The compounds of this invention are indazole derivatives having the following structure: (I), wherein R_1, R_2 and A are as defined herein. Such compounds have utility in the treatment of a wide range of conditions that are responsive to JNK inhibition. Thus, methods of treating such conditions are also disclosed, as are pharmaceutical compositions containing one or more compounds of the above compounds.

INDAZOLE DERIVATIVES AS JNK INHIBITORS AND COMPOSITIONS AND METHODS RELATED THERETO

This application claims the benefit of U.S. Provisional Application No. 60/221,799, filed July 31, 2000.

1. FIELD OF THE INVENTION

This invention is generally directed to indazole derivatives useful as Jun N-terminal kinase (JNK) inhibitors, compositions comprising the indazole derivatives and methods for their use.

2. BACKGROUND OF THE INVENTION

The Jun N-terminal kinase (JNK) pathway is activated by exposure of cells to environmental stress or by treatment of cells with pro-inflammatory cytokines. Targets of the JNK pathway include the transcription factors c-jun and ATF2 (Whitmarsh A.J., and Davis R.J. *J. Mol. Med.* 74:589-607, 1996). These transcription factors are members of the basic leucine zipper (bZIP) group that bind as homo- and hetero-dimeric complexes to AP-1 and AP-1-like sites in the promoters of many genes (Karin M., Liu Z.G. and Zandi E. *Curr. Opin. Cell Biol.* 9:240-246, 1997). JNK binds to the N-terminal region of c-jun and ATF-2 and phosphorylates two sites within the activation domain of each transcription factor (Hibi M., Lin A., Smeal T,, Minden A., Karin M. *Genes Dev.* 7:2135-2148, 1993; Mohit A.A., Martin M.H., and Miller C.A. *Neuron* 14:67-75, 1995). Three JNK enzymes have been identified as products of distinct genes (Hibi et al, *supra;* Mohit et al., *supra*). Ten different isoforms of JNK have been identified. These represent alternatively spliced forms of three different genes: JNK1, JNK2 and JNK3. JNK1 and 2 are ubiquitously expressed in human tissues, whereas JNK3 is selectively expressed in the brain, heart and testis (Dong C., Yang D., Wysk M., Whitmarsh A., Davis R., Flavell R. *Science* 270:1-4, 1998). Gene transcripts are alternatively spliced to produce four-JNK1 isoforms, four-JNK2 isoforms and two-JNK3 isoforms. JNK1 and 2 are expressed widely in mammalian tissues, whereas JNK3 is expressed almost exclusively in the brain. Selectivity of JNK signaling is achieved via specific interactions of JNK pathway components and by use of scaffold proteins that selectively bind multiple components of the signaling cascade. JIP-1 (JNK-interacting protein-1) selectively binds the MAPK module, MLK → JNKK2 → JNK. It has no binding

affinity for a variety of other MAPK cascade enzymes. Different scaffold proteins are likely to exist for other MAPK signaling cascades to preserve substrate specificity.

JNKs are activated by dual phosphorylation on Thr-183 and Tyr-185. JNKK1 (also known as MKK 4) and JNKK2 (MKK7), two MAPKK level enzymes, can mediate JNK activation in cells (Lin A., Minden A., Martinetto H., Claret F.-Z., Lange-Carter C., Mercurio F., Johnson G.L., and Karin M. *Science* 268:286-289, 1995; Tournier C., Whitmarsh A.J., Cavanagh J., Barrett T., and Davis R.J. *Proc. Nat. Acad. Sci. USA* 94:7337-7342, 1997). JNKK2 specifically phosphorylates JNK, whereas JNKK1 can also phosphorylate and activate p38. Both JNKK1 and JNKK2 are widely expressed in mammalian tissues. JNKK1 and JNKK2 are activated by the MAPKKK enzymes, MEKK1 and 2 (Lange-Carter C.A., Pleiman C.M., Gardner A.M., Blumer K.J., and Johnson G.L. *Science* 260:315-319, 1993; Yan M., Dai J.C., Deak J.C., Kyriakis J.M., Zon L.I., Woodgett J.R., and Templeton D.J. *Nature* 372:798-781, 1994). Both MEKK1 and MEKK2 are widely expressed in mammalian tissues.

Activation of the JNK pathway has been documented in a number of disease settings, providing the rationale for targeting this pathway for drug discovery. In addition, molecular genetic approaches have validated the pathogenic role of this pathway in several diseases. For example, autoimmune and inflammatory diseases arise from the over-activation of the immune system. Activated immune cells express many genes encoding inflammatory molecules, including cytokines, growth factors, cell surface receptors, cell adhesion molecules and degradative enzymes. Many of these genes are regulated by the JNK pathway, through activation of the transcription factors AP-1 and ATF-2, including TNFα, IL-2, E-selectin and matrix metalloproteinases such as collagenase-1 (Manning A.M. and Mercurio F. *Exp. Opin Invest. Drugs* 6: 555-567, 1997). Monocytes, tissue macrophages and tissue mast cells are key sources of TNFα production. The JNK pathway regulates TNFα production in bacterial lipopolysaccharide-stimulated macrophages, and in mast cells stimulated through the FceRII receptor (Swantek J.L., Cobb M.H., Geppert T.D. *Mol. Cell. Biol.* 17:6274-6282, 1997; Ishizuka T., Tereda N., Gerwins P., Hamelmann E., Oshiba A., Fanger G.R., Johnson G.L., and Gelfland E.W. *Proc. Nat. Acad. Sci. USA* 94:6358-6363, 1997). Inhibition of JNK activation effectively modulates TNFα secretion from these cells. The JNK pathway therefore regulates production of this key pro-inflammatory cytokine. Matrix metalloproteinases (MMPs) promote cartilage and bone erosion in rheumatoid arthritis, and generalized tissue destruction in other autoimmune diseases. Inducible expression of MMPs, including MMP-3 and MMP-9, type II and IV collagenases, are regulated via activation of the JNK pathway and AP-1 (Gum R., Wang H., Lengyel E.,

Juarez J., and Boyd D). *Oncogene* 14:1481-1493, 1997). In human rheumatoid synoviocytes activated with TNFα, IL-1, or Fas ligand the JNK pathway is activated (Han Z., Boyle D.L., Aupperle K.R., Bennett B., Manning A.M., Firestein G.S. *J. Pharm. Exp. Therap.* 291:1-7, 1999; Okamoto K., Fujisawa K., Hasunuma T., Kobata T., Sumida T., and Nishioka K. *Arth & Rheum* 40: 919-26, 1997). Inhibition of JNK activation results in decreased AP-1 activation and collagenase-1 expression (Han et al., *supra*). The JNK pathway therefore regulates MMP expression in cells involved in rheumatoid arthritis.

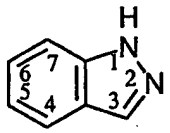
Inappropriate activation of T lymphocytes initiates and perpetuates many autoimmune diseases, including asthma, inflammatory bowel disease and multiple sclerosis. The JNK pathway is activated in T cells by antigen stimulation and CD28 receptor co-stimulation and regulates production of the growth factor IL-2 and cellular proliferation (Su B., Jacinto E., Hibi M., Kallunki T., Karin M., Ben-Neriah Y. *Cell* 77:727-736, 1994; Faris M., Kokot N., Lee L., and Nel A.E. *J. Biol. Chem.* 271:27366-27373, 1996). Peripheral T cells from mice genetically deficient in JNKK1 show decreased proliferation and IL-2 production after CD28 co-stimulation and PMA / Ca2+ ionophore activation, providing important validation for the role of the JNK pathway in these cells (Nishina H., Bachmann M., Oliveria-dos-Santos A.J., et al. *J. Exp. Med.* 186: 941-953, 1997). It is known that T cells activated by antigen receptor stimulation in the absence of accessory cell-derived co-stimulatory signals lose the capacity to synthesize IL-2, a state called clonal anergy. This is an important process by which auto-reactive T cell populations are eliminated from the peripheral circulation. Of note, anergic T cells fail to activate the JNK pathway in response to CD3- and CD28-receptor co-stimulation, even though expression of the JNK enzymes is unchanged (Li W., Whaley C.D., Mondino A., and Mueller D.L. *Science* 271: 1272-1276, 1996). Recently, the examination of JNK-deficient mice revealed that the JNK pathway plays a key role in T cell activation and differentiation to T helper 1 and 2 cell types. JNK1 or JNK2 knockout mice develop normally and are phenotypically unremarkable. Activated naïve CD4+ T cells from these mice fail to produce IL-2 and do not proliferate well (Sabapathy, K, Hu, Y, Kallunki, T, Schreiber, M, David, J-P, Jochum, W, Wagner, E, Karin, M. *Curr Biol* 9:116-125, 1999). It is possible to induce T cell differentiation in T cells from these mice, generating Th1 cells (producers of IFN-g and TNFβ) and Th2 effector cells (producers of IL-4, IL-5, IL-6, IL-10 and IL-13). Deletion of either JNK1 or JNK2 in mice resulted in a selective defect in the ability of Th1 effector cells to express IFNg. This suggests that JNK1 and JNK2 do not have redundant functions in T cells and that they play different roles in the control of cell growth, differentiation and death. The JNK pathway therefore, is an important point for regulation of T cell responses to antigen.

Cardiovascular disease ("CVD") accounts for nearly one quarter of total annual deaths worldwide. Vascular disorders such as atherosclerosis and restenosis result from dysregulated growth of the vessel wall, restricting blood flow to vital organs. The JNK pathway is activated by atherogenic stimuli and regulates local cytokine and growth factor production in vascular cells (Yang DD, Conze D, Whitmarsh AJ, et al, *Immunity;* 9:575, 1998). In addition, alterations in blood flow, hemodynamic forces and blood volume lead to JNK activation in vascular endothelium, leading to AP-1 activation and pro-atherosclerotic gene expression (Aspenstrom P., Lindberg U., and Hall A. *Curr. Biol.* 6:70-77, 1996). Ischemia and ischemia coupled with reperfusion in the heart, kidney or brain result in cell death and scar formation, which can ultimately lead to congestive heart failure, renal failure or cerebral dysfunction. In organ transplantation, reperfusion of previously ischemic donor organs results in acute leukocyte-mediated tissue injury and delay of graft function. The JNK pathway is activated by ischemia and reperfusion (Li Y., Shyy J., Li S., Lee J., Su B., Karin M., Chien S *Mol. Cell. Biol.* 16:5947-5954, 1996), leading to the activation of JNK-responsive genes and leukocyte-mediated tissue damage. In a number of different settings JNK activation can be either pro- or anti-apoptotic. JNK activation is correlated with enhanced apoptosis in cardiac tissues following ischemia and reperfusion (Pombo CM, Bonventre JV, Avruch J, Woodgett JR, Kyriakis J.M, Force T. *J. Biol. Chem.* 269:26546-26551, 1994).

Cancer is characterized by uncontrolled growth, proliferation and migration of cells. Cancer is the second leading cause of death with 500,000 deaths and an estimated 1.3 million new cases in the United States in 1996. The role of signal transduction pathways contributing to cell transformation and cancer is a generally accepted concept. The JNK pathway leading to AP-1 appears to play a critical role in cancer. Expression of c-jun is altered in early lung cancer and may mediate growth factor signaling in non-small cell lung cancer (Yin T., Sandhu G., Wolfgang C.D., Burrier A., Webb R.L., Rigel D.F. Hai T., and Whelan J. *J. Biol. Chem.* 272:19943-19950, 1997). Indeed, over-expression of c-jun in cells results in transformation, and blocking c-jun activity inhibits MCF-7 colony formation (Szabo E., Riffe M., Steinberg S.M., Birrer M.J., Linnoila R.I. *Cancer Res.* 56:305-315, 1996). DNA-damaging agents, ionizing radiation and tumor necrosis factor activate the JNK pathway. In addition to regulating c-jun production and activity, JNK activation can regulate phosphorylation of p53, and thus can modulate cell cycle progression (Chen T.K., Smith L.M., Gebhardt D.K., Birrer M.J., Brown P.H. *Mol. Carcinogenesis* 15:215-226, 1996). The oncogene BCR-Abl, associated with t(9,22) Philadelphia chromosome translocation of chronic myelogenous leukemia, activates JNK and leads to transformation of hematopoietic

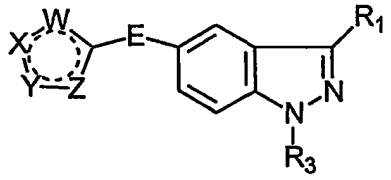
cells (Milne D.M., Campbell L.E., Campbell D.G., Meek D.W. *J. Biol. Chem.* 270:5511-5518, 1995). Selective inhibition of JNK activation by a naturally occurring JNK inhibitory protein, called JIP- 1, blocks cellular transformation caused by BCR-Abl expression (Raitano A.B., Halpern J.R., Hambuch T.M., Sawyers C.L. *Proc. Nat. Acad. Sci USA* 92:11746-11750, 1995). Thus, JNK inhibitors may block transformation and tumor cell growth.

In general, the class of compounds known as "indazoles" is well known. More specifically, an "indazole" is a compound containing a fused, bicyclic ring system having the following structure:



Compounds of the above structure are typically referred to as "1*H*-indazole" due to the presence of the hydrogen atom at the 1-position.

EP Patent Application 0 494 774 Al discloses compounds of the following structure:



for use as agonists of the 5-hydroxytryptamine (5-HT) receptors. Such receptors exhibit selective vasoconstrictor activity, and the agonists of this published application are purported to have utility in the treatment of migraine, cluster headache, chronic paraxysmal hemicrania and headaches associated with vascular disorders. 1H-indazoles have also been made for synthetic and mechanistic studies, and as intermediates in the synthesis of other potential therapeutics. For example, the following references disclose 3-phenyl-5-methyl-1H-indazole: *Pharmazie 54(2)*:99-101, 1999; *Dopov. Akad. Nauk Ukr. 8*:126-31, 1994; *Pokl. Akad. Nauk SSSR 305(6)*:1378-81, 1989; *Yakugaku Zasshi 106(11)*:1002-7, 1986 (also reports 5-Ph-3-CHO derivative); *Yakugaku Zasshi 106(11)*:995-1001, 1986; *Heterocycles 24(10)*:2771-5, 1986; JP 60/004184; JP 60/004185; EP 23633; *J. Org. Chem. 43(10)*:2037-41, 1978 (also reports 3-(4-Me-Ph)-5-Me derivative); JP 60/004824; JP 59/036627;

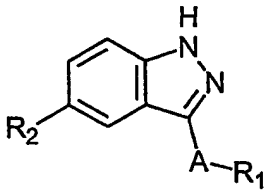
US 3,994,890; JP 58/030313; JP 60/003063. Additional 3-phenyl indazoles with the indicated 5-substituents are disclosed in the following references: EP 55450 (CHO); U.S. 5,760,028 and WO 97/23480 (CO_2Et; also disclose 3-C≡CPh-5-CO_2Et derivative); DE 1266763 and *Justus Liebigs Ann. Chem.* 697:17-41, 1966 (OMe). EP 470039 discloses the 3-(4-fluorophenyl)-5-trifluoromethyl indazole, and *Heterocycles (36(11)* :2489-95, 1993) discloses the 3-(6,7-dimethoxyisoquinolin-1-yl)-5-hydroxy derivative.

Accordingly, there is a need in the art for selective inhibitors of JNK. In addition, there is a need for pharmaceutical compositions comprising one or more inhibitors, as well as for methods for treating conditions in animals which are responsive to such inhibitors. The present invention fulfills these needs, and provides further related advantages.

3. SUMMARY OF THE INVENTION

In brief, the present invention is directed to novel compounds having activity as selective inhibitors of JNK, and to compositions and methods related thereto.

The novel compounds of the present invention may generally be classified as "indazole derivatives" having the following structure (I):



(I)

wherein A, R_1 and R_2 are as defined below, including isomers, prodrugs and pharmaceutically acceptable salts thereof.

The present invention is also directed to methods for treating a variety of conditions by administering an effective amount of a compound of structure (I) to an animal or subject in need thereof (referred to herein as a "patient"), typically a warm-blooded animal (including a human). Prior to administration, one or more compounds of this invention are typically formulated as a pharmaceutical composition which contains an effective dosage amount of one or more of such compounds in combination with one (or more) pharmaceutically acceptable carrier(s). Conditions that may be treated by the compounds of this invention, or a pharmaceutical composition containing the same, include any condition which may benefit from administration of JNK inhibitors, and are particularly useful for the prevention and/or treatment of various diseases including (but not limited to) rheumatoid

arthritis; rheumatoid spondylitis; osteoarthritis; gout; asthma, bronchitis; allergic rhinitis; chronic obstructive pulmonary disease; cystic fibrosis; inflammatory bowel disease; irritable bowel syndrome; mucous colitis; ulcerative colitis; Crohn's disease; Huntington's disease; gastritis; esophagitis; hepatitis; pancreatitis; nephritis; multiple sclerosis; lupus erythematosus; Type II diabetes; atherosclerosis; restenosis following angioplasty; left ventricular hypertrophy; myocardial infarction; stroke; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen and brain; acute or chronic organ transplant rejection; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; multiple organ failure; psoriasis; burn from exposure to fire, chemicals or radiation; eczema; dermatitis; skin graft; ischemia; ischemic conditions associated with surgery or traumatic injury; epilepsy; Alzheimer's disease; Parkinson's disease; immunological response to bacterial or viral infection; cachexia; angiogenic and proliferative dieseases; solid tumor; and cancers of a variety of tissues such as colon, rectum, prostate, liver, lung, bronchus, pancreas, brain, head, neck, stomach, skin, kidney, cervix, blood, larynx, esophagus, mouth, pharynx, urinary bladder, ovary or uterine.

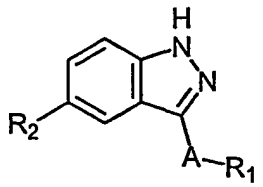
The compounds described herein could also be useful as an adjunct to existing and/or experimental therapies.

These and other aspects of this invention will be evident upon reference to the following detailed description. To that end, certain patent and other documents are cited herein to more specifically set forth various aspects of this invention. Each of these documents are hereby incorporated by reference in their entirety.

4. DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention is directed to novel compounds which have activity as selective inhibitors of JNK. This invention is also directed to compositions and methods relating to the same.

The compounds of this invention have the following structure (I):



(I)

including isomers, prodrugs and pharmaceutically acceptable salts thereof,

wherein:

A is a direct bond, $-(CH_2)_a-$, $-(CH_2)_bCH=CH(CH_2)_c-$, or $-(CH_2)_bC\equiv C(CH_2)_c-$;

R_1 is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R_3;

R_2 is $-R_3$, $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_aR_5$ or $-(CH_2)_bSO_2NR_5R_6$;

a is 1, 2, 3, 4, 5 or 6;

b and *c* are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

d is at each occurrence 0, 1 or 2;

R_3 is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocycloalkyl, substituted heterocyclealkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-CN$, $-NO_2$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;

R_4 is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from R_3, or R_4 is halogen or hydroxy;

R_5, R_6 and R_7 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of R_5, R_6 and R_7 are optionally substituted with one to four substituents independently selected from R_3; and

R_8 and R_9 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or R_8 and R_9 taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of R_8, R_9, and R_8 and R_9 taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from R_3;

with the proviso that:

when A is a direct bond and R_1 is phenyl,

R_2 is not methyl, methoxy, $C(=O)CH_3$ or $C(=O)H$;

when A is a direct bond and R_1 is 4-Me-phenyl,

R_2 is not methyl;

when A is a direct bond and R_1 is 4-F-phenyl,

R_2 is not trifluoromethyl;

when A is a direct bond or -C≡C- and R_1 is phenyl,

R_2 is not -COOEt; and

when A is a direct bond and R_1 is 6,7-dimethoxyisoquinolin-1-yl,

R_2 is not hydroxy.

In one embodiment, -A-R_1 is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein *b* is 2 or 3 and wherein R_8 and R_9 are defined above.

In another embodiment, R_2 is $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$, and *b* is an integer ranging from 0-4.

In another embodiment, R_2 is $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bNR_5C(=O)R_6$, 3-triazolyl or 5-tetrazolyl, wherein *b* is 0 and wherein R_8 and R_9 are defined above.

In a preferred embodiment, R_2 is 3-triazolyl or 5-tetrazolyl.

In another preferred embodiment:

(a) -A-R_1 is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein *b* is 2 or 3; and

(b) R_2 is $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bNR_5C(=O)R_6$, 3-triazolyl or 5-tetrazolyl, wherein *b* is 0 and wherein R_8 and R_9 are defined above.

In a more preferred embodiment:

(a) -A-R_1 is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein *b* is 2 or 3; and

(b) R_2 is 3-triazolyl or 5-tetrazolyl.

In another preferred embodiment, R_2 is R_4, and R_4 is 3-triazolyl, optionally substituted at its 5-position with:

(a) a C_1-C_4 straight or branched chain alkyl group optionally substituted with a hydroxyl, methylamino, dimethylamino or 1-pyrrolidinyl group; or

(b) a 2-pyrrolidinyl group.

In a more preferred embodiment, R_2 is R_4, and R_4 is methyl, n-propyl, isopropyl, 1-hydroxyethyl, 3-hydroxypropyl, methylaminomethyl, dimethylaminomethyl, 1-(dimethylamino)ethyl, 1-pyrrolidinylmethyl or 2-pyrrolidinyl.

As used herein, the terms used above having following meaning.

"Alkyl" means a straight chain or branched, saturated or unsaturated alkyl, cyclic or non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (also referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1 butynyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cycloalkyls are also referred to herein as "carbocyclic" rings systems, and include bi- and tri-cyclic ring systems having from 8 to 14 carbon atoms such as a cycloalkyl (such as cyclopentane or cyclohexane) fused to one or more aromatic (such as phenyl) or non-aromatic (such as cyclohexane) carbocyclic rings.

"Halogen" means fluorine, chlorine, bromine or iodine.

"Keto" means a carbonyl group *(i.e.,* C=O).

"Aryl" means an aromatic carbocyclic moiety such as phenyl or naphthyl.

"Acyloxy means an -OC(O)alkyl group, wherein "alkyl" is defined above.

"Arylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with an aryl moiety, such as benzyl, $-(CH_2)_2$phenyl, $-(CH_2)_3$phenyl, $-CH(phenyl)_2$, and the like.

"Heteroaryl" means an aromatic heterocycle ring of 5- to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl.

"Heteroarylalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heteroaryl moiety, such as -CH_2pyridinyl, -CH_2pyrimidinyl, and the like.

"Heterocycle" means a heterocyclic ring containing from 5 to 10 ring atoms

"Heterocycle" means a 5- to 7-membered monocyclic, or 7- to 10-membered bicyclic, heterocyclic ring which is either saturated, unsaturated, or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the heteroaryls listed above, heterocycles also include morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocycloalkyl" means an alkyl having at least one alkyl hydrogen atom replaced with a heterocycle, such as -CH_2morpholinyl, and the like.

The term "substituted" as used herein means any of the above groups *(i.e.,* aryl, arylalkyl, heterocycle and heterocycloalkyl) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent, two hydrogen atoms are replaced. Substituents include halogen, hydroxyl, alkyl, substituted alkyl (such as haloalkyl, mono- or di-substituted aminoalkyl, alkyloxyalkyl, and the like), aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocycloalkyl, substituted heterocycloalkyl, $-NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)NR_aR_b$, $-NR_aC(=O)OR_b$ $-NR_aSO_2R_b$, $-OR_a$, $-C(=O)R_a$ $C(=O)OR_a$ $-C(=O)NR_aR_b$, $-OC(=O)R_a$, $-OC(=O)OR_a$, $-OC(=O)NR_aR_b$, $-NR_aSO_2R_b$, or a radical of the formula -Y-Z-R_a where Y is alkanediyl, substituted alkanediyl, or a direct bond, Z is -O-, -S-, $-N(R_b)-$, -C(=O)-, -C(=O)O-, -OC(=O)-, $-N(R_b)C(=O)-$, $-C(=O)N(R_b)-$ or a direct bond, wherein R_a and R_b are the same or different and independently hydrogen, amino, alkyl, substituted alkyl (including halogenated alkyl), aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocylealkyl or substituted heterocycloalkyl, or wherein R_a and R_b taken together with the nitrogen atom to which they are attached form a heterocycle or substituted heterocycle.

"Haloalkyl" means alkyl having one or more hydrogen atoms replaced with halogen, such as $-CF_3$.

"Hydroxyalkyl" means alkyl having one or more hydrogen atoms replaced with hydroxy, such as $-CH_2OH$

"Sulfonylalkyl" means $-SO_2$-(alkyl), wherein "alkyl" is defined above;

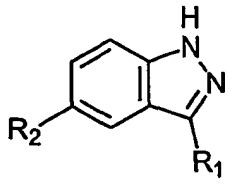
"Sulfinylalkyl" means -SO-(alkyl), wherein "alkyl" is defined above;

"Thioalky" means -S-(alkyl), wherein "alkyl" is defined above;

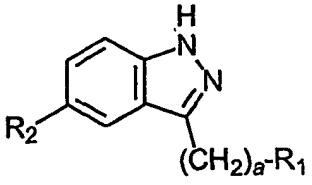
"Carboxyl" means -COOH.

"Alkoxy" means -O-(alkyl), wherein "alkyl" is defined above.

In one embodiment, compounds of this invention have structure (II) when A is a direct bond, and have structure (III) when A is $-(CH_2)_a$-:

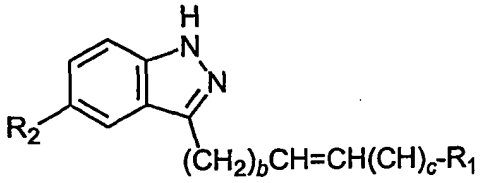


(II)

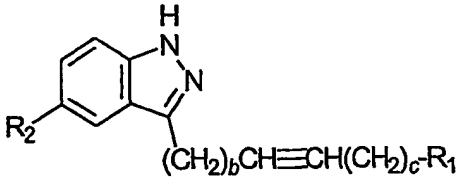


(III)

In other embodiments, compounds of this invention have structure (IV) when A is a $-(CH_2)_bCH=CH(CH_2)_c$-, and have structure (V) when A is $-(CH_2)_bC\equiv C(CH_2)_c$-:

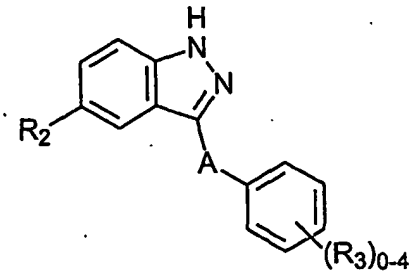


(IV)



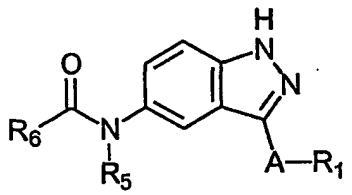
(V)

In further embodiments of this invention, R_1 is aryl or substituted aryl, such as phenyl or substituted phenyl as represented by the following structure (VI):



(VI)

In another embodiment, R_2 is $-(CH_2)_bNR_4(C=O)R_5$. In one aspect of this embodiment, b =0 and compounds of this invention have the following structure (VII):



(VII)

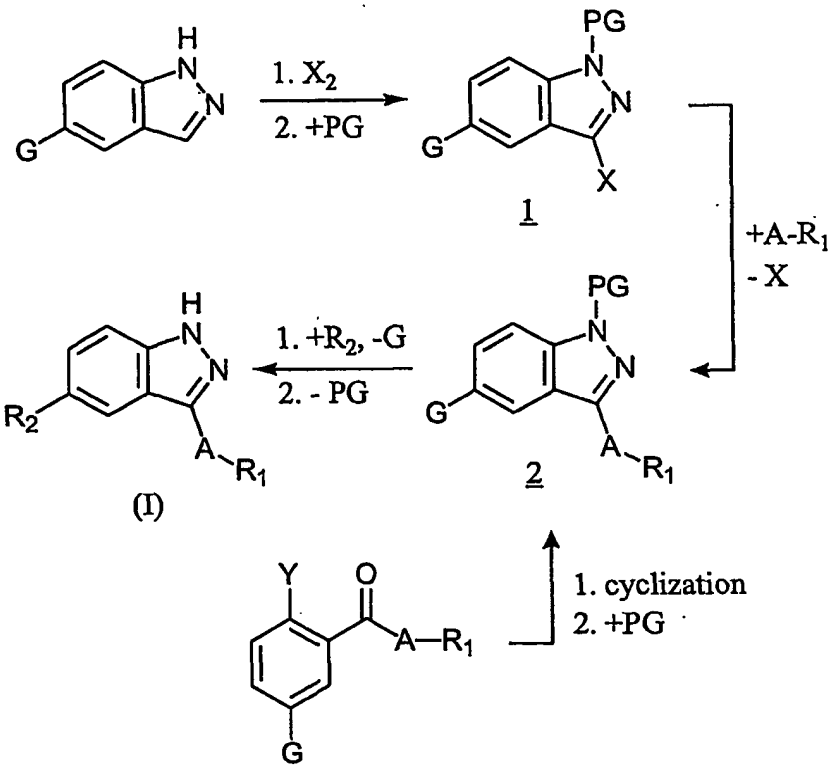
Representative R_2 groups of this invention include alkyl (such as methyl and ethyl), halo (such as chloro and fluoro), haloalkyl (such as trifluoromethyl), hydroxy, alkoxy (such as methoxy and ethoxy), amino, arylalkyloxy (such as benzyloxy), mono- or di-alkylamine (such as $-NHCH_3$, $-N(CH_3)_2$ and $-NHCH_2CH_3$), $-NHC(=O)R_4$ wherein R_6 is a substituted or unsubstituted phenyl or heteroaryl (such as phenyl or heteroaryl substituted with hydroxy, carboxy, amino, alkylester, alkoxy, alkyl, aryl, haloalkyl, halo, $-CONH_2$ and -CONH alkyl), -NH(heteroarylalkyl) (such as $-NHCH_2$(3-pyridyl), $-NHCH_2$(4-pyridyl), heteroaryl (such as pyrazolo, triazolo and tetrazolo), $-C(=O)NHR_6$ wherein R_6 is hydrogen, alkyl, or as defined above (such as $-C(=O)NH_2$, $-C(=O)NHCH_3$, -C(=O)NH(H-carboxyphenyl), $-C(=O)N(CH_3)_2$), arylalkenyl (such as phenylvinyl, 3-nitrophenylvinyl, 4-carboxyphenylvinyl), heteroarylalkenyl (such as 2-pyridylvinyl, 4-pyridylvinyl).

Representative R_3 groups include halogen (such as chloro and fluoro), alkyl (such as methyl, ethyl and isopropyl), haloalkyl (such as trifluoromethyl), hydroxy, alkoxy (such as methoxy, ethoxy, n-propyloxy and isobutyloxy), amino, mono- or di-alkylamino (such as dimethylamine), aryl (such as phenyl), carboxy, nitro, cyano, sulfinylalkyl (such as methylsulfinyl), sulfonylalkyl (such as methylsulfonyl), sulfonamidoalkyl (such as $-NHSO_2CH_3$), $-NR_8C(=O)(CH_2)_bOR_9$ (such as $-NHC(=O)CH_2OCH_3$), $NHC(=O)R_9$ (such as

-NHC(=O)CH_3, -NHC(=O)$CH_2C_6H_5$, -NHC(=O)(2-furanyl)), and -O$(CH_2)_b$$NR_8R_9$ (such as -O$(CH_2)_2$$N(CH_3)_2$).

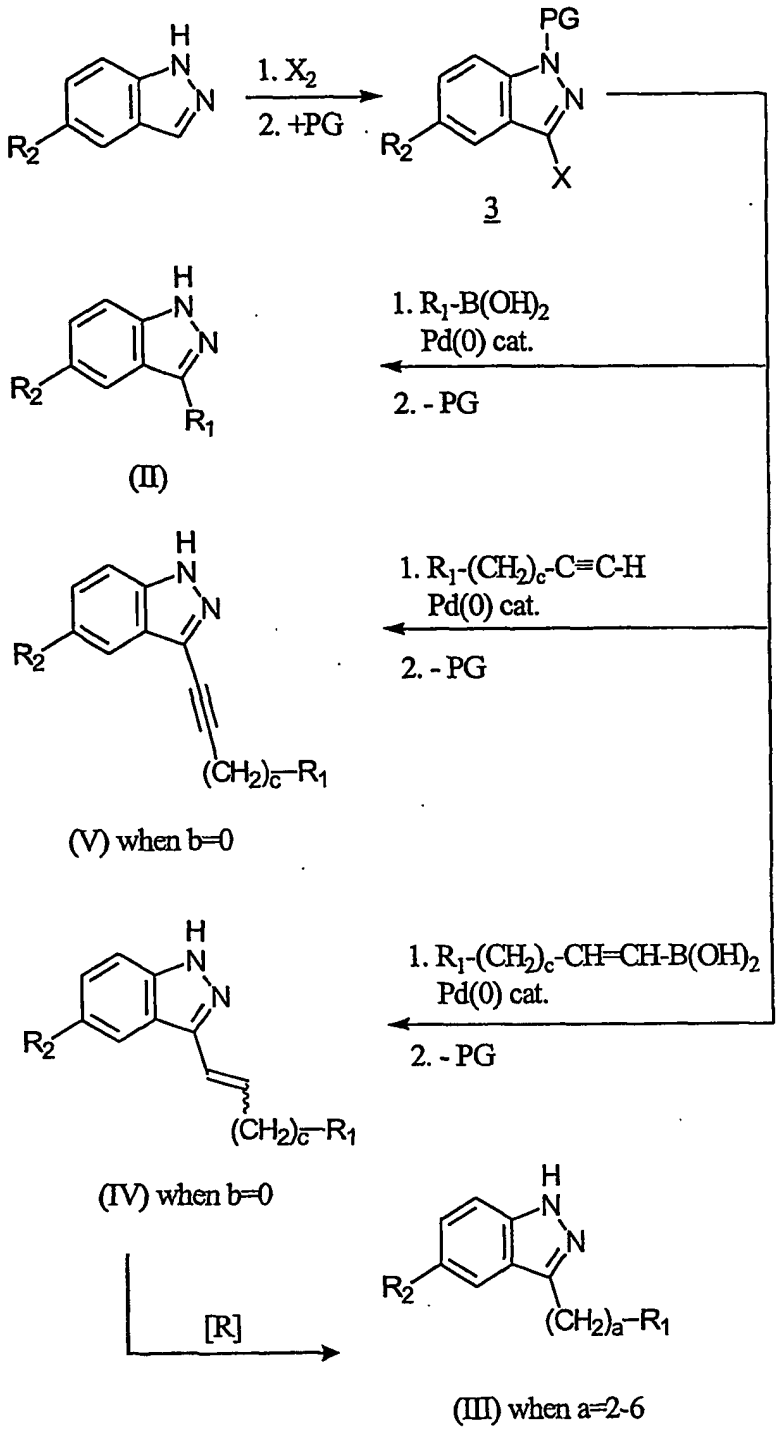
The compounds of this invention may generally be made by organic synthesis techniques known to those skilled in the art, as well as by the following general techniques and by the procedures set forth in the Examples. To that end, the compounds of this invention may be made according to the following Reaction Schemes 1 through 7 (it should be noted that, in the following reaction schemes, hydrogen atoms are sometimes not depicted and one skilled in organic chemistry would appreciate such accepted shorthand notation):

Reaction Scheme 1



In Reaction Scheme 1, indazoles of this invention may be prepared by techniques well known to those skilled in the art of organic synthesis. Starting from an appropriately 5-substituted indazole, the 3-position may be activated for substitution by use of a suitable dihalogen (X_2). If necessary, a protecting group is then added to the nitrogen at the 1-position (N-1) to give 1. The halogen may be displaced by an appropriately activated A-R_1 moiety to give 2; see, *e.g.*, Reaction Schemes 2 and 5. Alternatively, an appropriately substituted phenyl ketone may be cyclized to give indazole 2 see, *e.g.*, Reaction Schemes 3 and 4. The G moiety may then be left unchanged, displaced or transformed into the desired R_2; see, *e.g.*, Reaction Schemes 3 through 6. Deprotection of N-1 gives indazoles of structure (I).

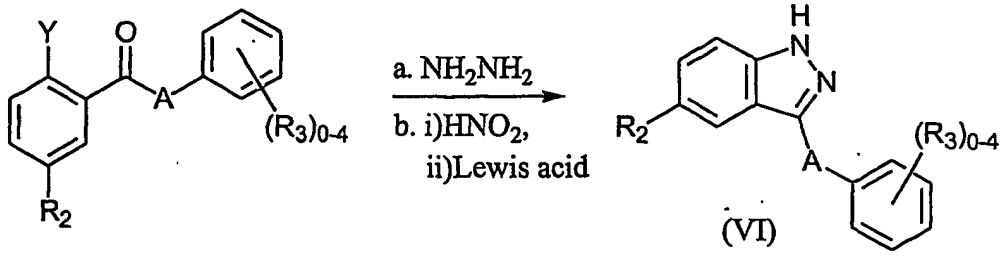
Reaction Scheme 2



Reaction Scheme 2 illustrates synthetic sequences that yield compounds containing various A moieties. Suitable starting materials are commercially available indazoles with the desired R_2 or may be readily prepared, *e.g.*, as in Reaction Schemes 5 and 6. The starting indazole is halogenated at the 3-position with a suitable reagent, *e.g.*, Br_2. It is then protected at N-1 with any suitable nitrogen protecting group to give 3. Suitable protecting groups include but are not limited to acetyl, methoxyethoxymethyl and tetrahydropyranyl. Indazoles, wherein A is a direct bond, may be produced from 3 by displacement of the halogen with an appropriately activated R_1 moiety. For example, in the presence of a suitable Pd(0) or Pd(II) catalyst, R_1-boronic acids may be coupled via a Suzuki reaction to give, after deprotection, compound (II). Analogously, compounds (IV) and (V) may be prepared from suitable alkene and alkyne precursors in the presence of an appropriate Pd(0) catalyst. The cis isomer of indazole (IV) may also be prepared by partial reduction of (V) by, *e.g.*, hydrogenation over $BaSO_4$ that has been treated with quinoline. Compound (III) may be prepared from (IV) via reduction, *e.g.*, with hydrogen in the presence of Pd-C.

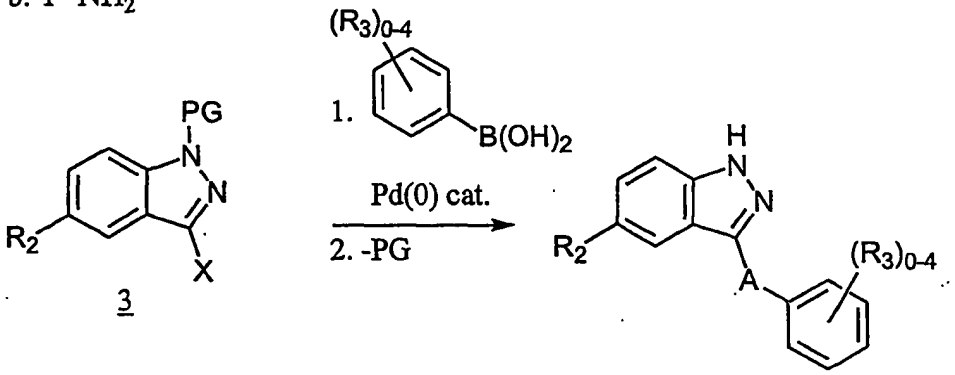
Reaction Scheme 3

A.



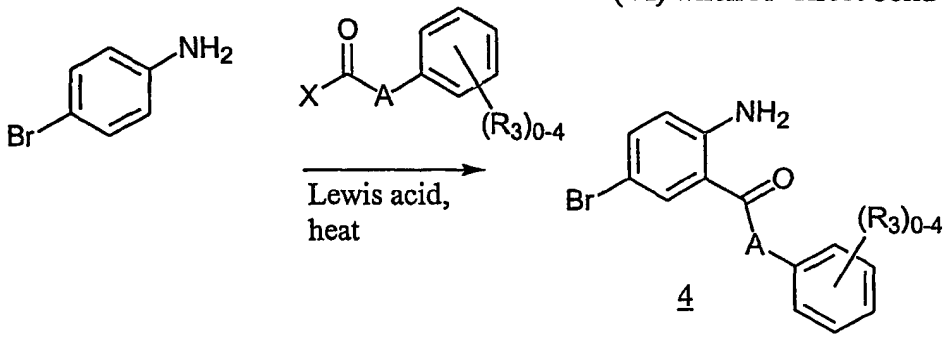
a. Y=leaving group (LG)
b. Y=NH_2

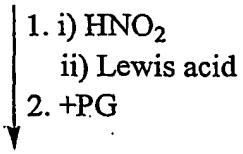
B.

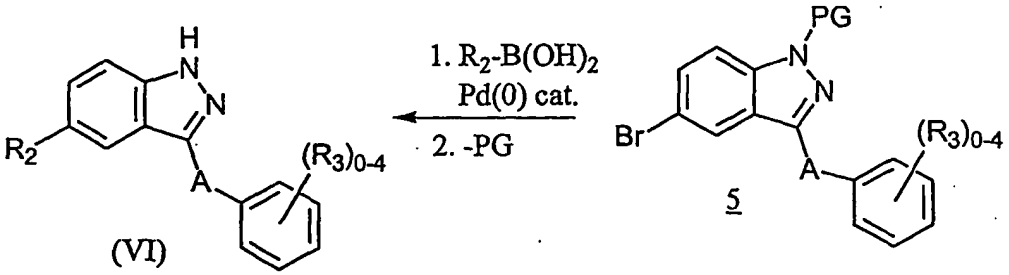


(VI) when A=direct bond

C.





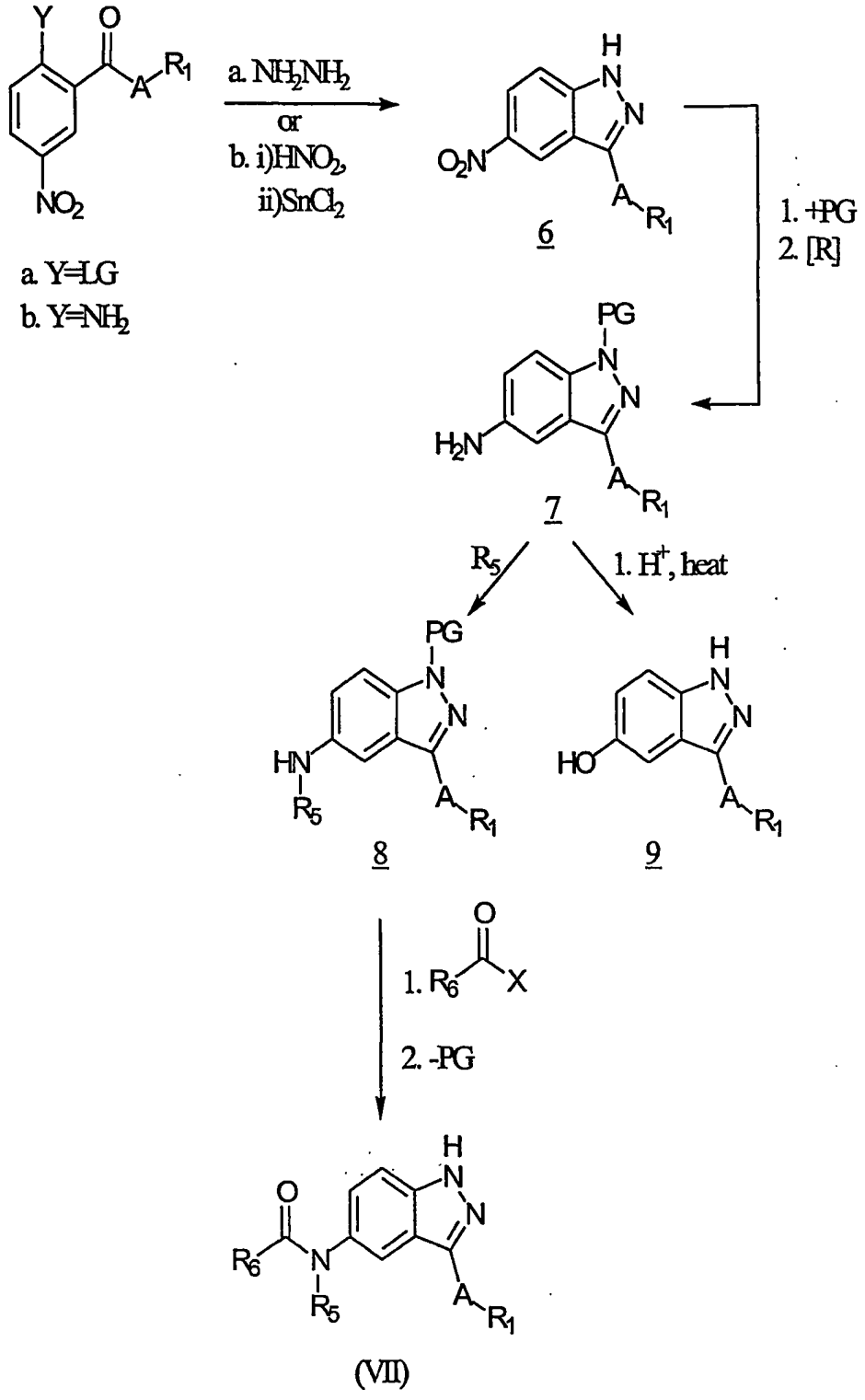


Reaction Scheme 3 illustrates several syntheses of compound (VI) wherein R_1 is depicted as a substituted phenyl group for purposes of illustration only. In Scheme 3A, a phenyl ketone, appropriately substituted at Y and R_2, serves as the starting material. When Y is an amino group, the starting material may be cyclized by exposure, first to HNO_2 and then to a reducing agent, such as $SnCl_2$, to give compound (VI). Alternatively, when Y is a leaving group such as halogen *(e.g.,* F or Cl), heating the phenyl ketone in the presence of hydrazine effects cyclization to indazole (VI).

In Scheme 3B, halogenated indazole 3 may be coupled with a suitable substituted phenyl moiety and deprotected to give compound (VI), wherein A is a direct bond. By way of example, a phenyl boronic acid substituted with 0-4 R_3 groups will react with a protected 3-bromo-1H-indazole in the presence of a Pd(II) catalyst to yield compound (VI).

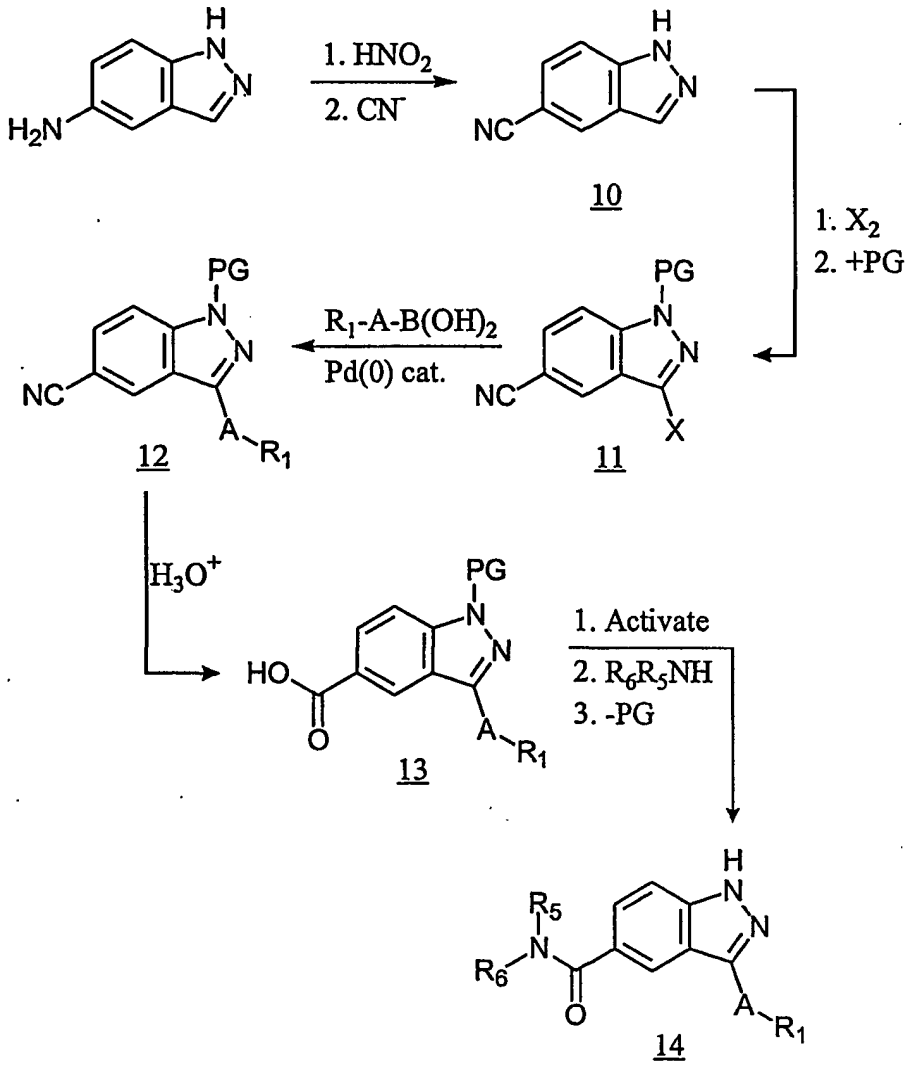
Scheme 3C illustrates an alternative synthesis of compound (VI) from the 5-halo-phenyl ketone; this route allows introduction of R_2 groups later in the sequence. 4-Bromo-aniline is acylated with a suitably activated A-R_1 moiety, heated in the presence of an appropriate Lewis acid such as $ZnCl_2$. For example, a suitably activated A-R_1 group is an acid halide such as carbonyl chloride. The resulting ketone 4 is cyclized as in Scheme 3A, and protected with appropriate groups at the N-1 position as in Scheme 2. The R_2 group may be introduced via a Pd-catalyzed coupling as in Scheme 2, and the protecting group removed to yield compound (VI).

Reaction Scheme 4



The synthesis of the embodiment wherein R_2 is an amino carbonyl-containing group is shown by Reaction Scheme 4. In analogy to Scheme 3A, a suitably substituted 4-nitro-phenyl ketone may be cyclized, depending on Y, by exposure either to hydrazine or to HNO_2 and a reducing agent. After protection of N-1, the nitro-group may be reduced by, *e.g.*, hydrogenation over Pd-C, to give 7. The resulting amine may optionally be substituted with R_4, by, *e.g.*, reductive amination, using procedures well known to one skilled in the art of organic synthesis. Compound 8 is acylated with a suitable activated carbonyl moiety and deprotected to give compound (VII). Alternatively, 7 may be hydrolyzed to the 5-hydroxy compound, 9.

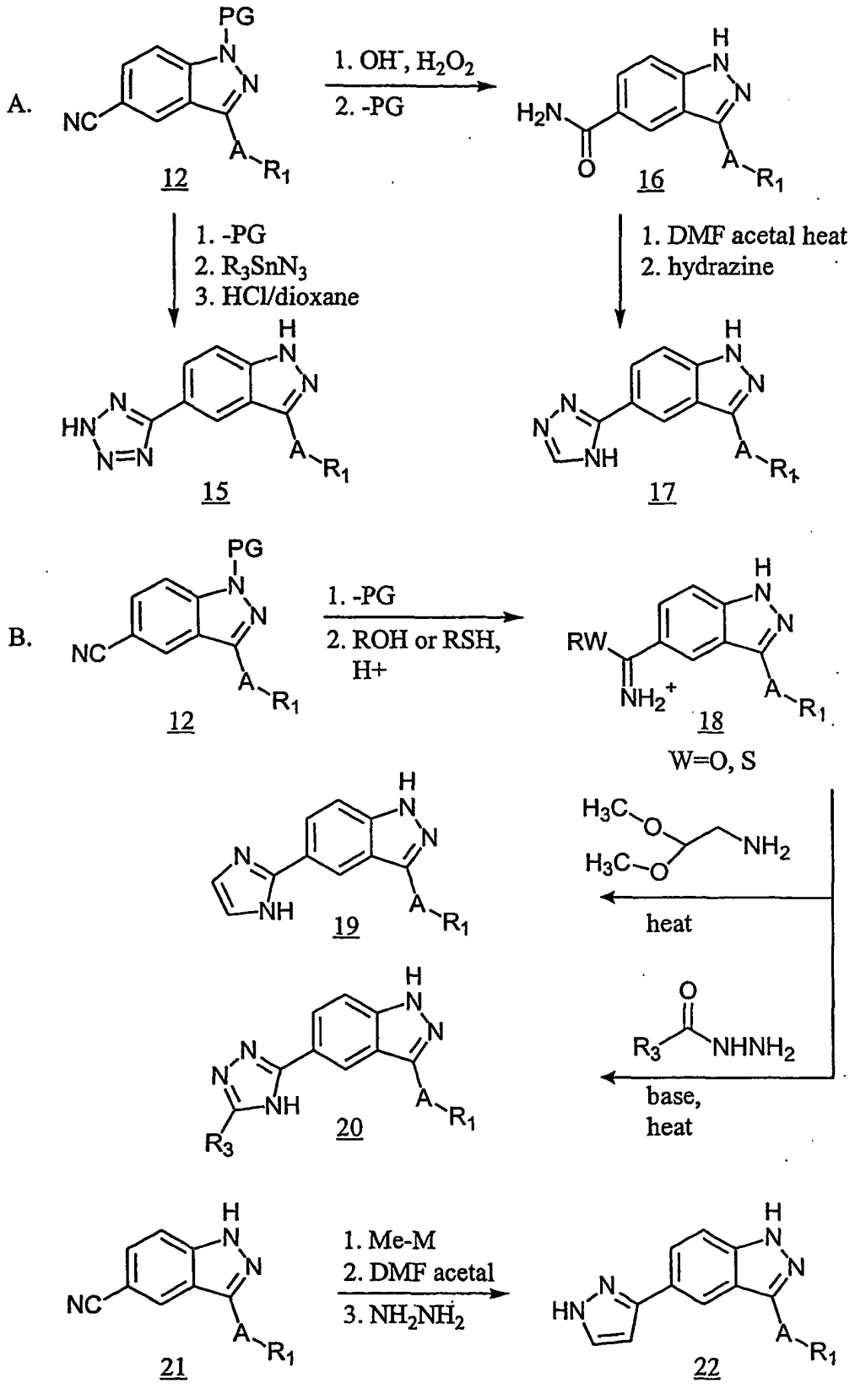
Reaction Scheme 5



Reaction Scheme 5 illustrates a synthetic route for the further embodiment of (I) wherein R_2 is a carboxamide. Commercially available 5-amino-1H-indazole is substituted with cyanide at the 5-position to give 10 by treatment with HNO_2, followed, after neutralization to ca. pH 7, by treatment with a cyanide source, *e.g.*, a mixture of CuCn and NaCN. Nitrile 10 may be activated at the 3-position, protected at N-1 and subsequently substituted with an appropriate A-R_1 moiety according to procedures of Scheme 2. The resulting compound, 12, may be hydrolyzed in aqueous acid to give carboxylate 13. Activation of 13 by a suitable method, followed by treatment with R_5R_4NH and deprotection gives the carboxamide, 14. Suitable activation methods include but are not limited to 1) conversion of the carboxylate to an acyl halide *(e.g.,* chloride) and coupling in the presence

of pyridine or a related base; and 2) use of a coupling agent suitable for amide bond formation *(e.g.,* dicyclohexylcarbodiimide).

Reaction Scheme 6



Reaction Scheme 6 illustrates the additional embodiment wherein R2 is a five-membered heterocyclic substituent. In Scheme 6A, nitrile 12 is deprotected at N-1 and converted to the tetrazole 15 by use of an electrophilic azide source *(e.g.,* a trialkyl tin such as $(Bu)_3SnN_3$). Nitrile 12 may also be converted to the unsubstituted triazole 17 in four steps. The nitrile is first transformed to the carboxamide by exposure to aqueous base under oxidizing conditions *(e.g.,* NaOH and H_2O_2). The N-1 protecting group is removed to give intermediate 16. The carboxamide is heated with DMF acetal and subsequently treated with hydrazine under acidic conditions to give the desired triazole.

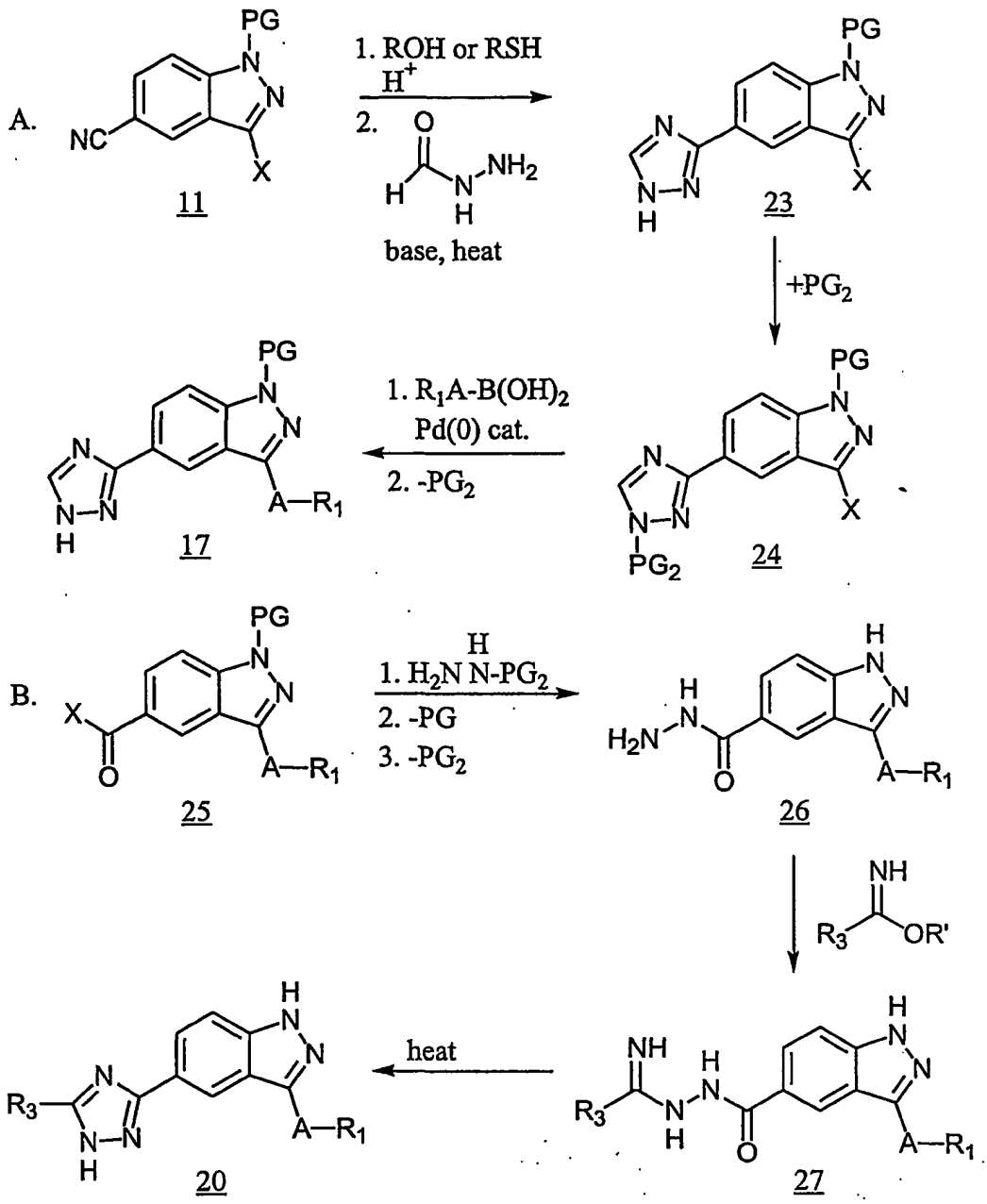
Scheme 6B illustrates the synthesis of imidazole and substituted triazole derivatives at R_2. Nitrile 12 is deprotected and converted to the imidate or thioimidate by heating in the appropriate alcohol or thiol under acidic conditions to give 18. Subsequent exposure to 1-amino-2,2-dimethoxyethane and gentle heating effects formation of imidazole 19. Alternatively, heating 18 with alkyl, aryl or heterocyclic hydrazides under basic conditions (*e.g.,* in presence of a tertiary organoamine such as triethylamine) results in production of 3-substituted triazole 20.

Pyrazole derivatives may be synthesized according to Scheme 6C. Nitrile 12 may be deprotected at N-1 to give starting material 21. Treatment of the latter nitrile with a suitable organometallic agent, *e.g.,* methyl lithium, yields a methyl ketone intermediate. Subsequent treatment by heating with DMF acetal followed by exposure to hydrazine gives pyrazole 22.

Scheme 7 depicts alternative routes to 5-triazole derivatives of 1H-indazoles. In scheme 7A nitrile 11 is converted to triazole 23 under conditions similar to those employed in Scheme 6B. A suitable protecting group, *e.g.,* trityl, is incorporated onto the free triazole nitrogen to give 24. A-R_1 is then added to position-3 by a boronic acid or other suitable derivative. Finally, the triazole protecting group is removed under, *e.g.,* acidic conditions, to give indazole 17.

In Scheme 7B, starting material 25 is prepared by activation of 13 as, *e.g.,* an acid halide such as chloride. Subsequent reaction with a protected hydrazide followed by removal of protecting groups yields hydrazide 26. By way of example, when PG = acetyl and PG_2 = t-butyl-oxycarbonyl, the protecting groups are removed by sequential treatment with ammonia followed by acid, *e.g.,* HCl. Indazole 26 is treated with an appropriate imidate to give 27 and converted to triazole 20 by heating in a polar solvent, *e.g.,* DMF.

Scheme 7


A.
PG
NC
X
11
1. ROH or RSH
H+
2.
O
NH2
H
N
H
base, heat
23
+PG2
24
PG2
1. R1A-B(OH)2
Pd(0) cat.
2. -PG2
17
A—R1
B.
X
O
25
1. H2N N-PG2
H
2. -PG
3. -PG2
26
H2N
NH
R3
OR'
27
heat
20

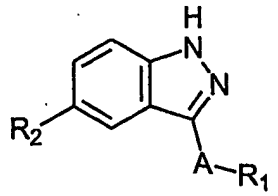
Pharmaceutically acceptable salts of compounds of structure (I) are also within the scope of this invention. To this end, the compound may generally be utilized as the free base. Alternatively, the compounds may be used in the form of acid addition salts. Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of a compound of structure (I) is intended to encompass any and all acceptable salt forms.

Pharmaceutically acceptable salts of this invention may be formed by conventional and known techniques, such as by reacting a compound of this invention with a suitable acid as disclosed above. Such salts are typically formed in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash in the final step of the synthesis. The salt-forming acid may dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound of this invention is desired in the free base form, it may be isolated from a basic final wash step, according to known techniques. For example, a typical technique for preparing hydrochloride salt is to dissolve the free base in a suitable solvent, and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it.

The compound of this invention may also exist in various isomeric forms, including configurational, geometric and conformational isomers, as well as existing in various tautomeric forms, particularly those that differ in the point of attachment of a hydrogen atom. As used herein, the term "isomer" is intended to encompass all isomeric forms of a compound, including tautomeric forms of the compound.

As used herein, the term "prodrug" refers to any derivative of indazoles of this invention that are metabolized or otherwise converted into an active form upon introduction into the body of an animal. Prodrugs are well known to those skilled in the art of pharmaceutical chemistry, and provide benefits such as increased adsorption and half-life. Prodrugs of this invention may be formed when, for example, hydroxy groups are esterified or alkylated, or when carboxyl groups are esterified. Those skilled in the art of drug delivery will readily appreciate that the pharmacokinetic properties of indazoles of this invention may be controlled by an appropriate choice of moieties to produce prodrug derivatives.

In another embodiment, the present invention provides a method for treating one or more of a variety of conditions by administering an effective amount of a compound of this invention to a patient in need thereof. In this embodiment, the compounds of this invention have the following structure (I):



(I)

including isomers, prodrugs and pharmaceutically acceptable salts thereof,

wherein:

A is a direct bond, $-(CH_2)_a-$, $-(CH_2)_bCH=CH(CH_2)_c-$, or $-(CH_2)_bC\equiv C(CH_2)_c-$;

R_1 is aryl, heteroaryl or heterocycle fused to phenyl, each being optionally substituted with one to four substituents independently selected from R_3;

R_2 is $-R_3$, $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$;

a is 1, 2, 3, 4, 5 or 6;

b and *c* are the same or different and at each occurrence independently selected from 0, 1, 2, 3 or 4;

d is at each occurrence 0, 1 or 2;

R_3 is at each occurrence independently halogen, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heterocycle, substituted heterocycle, heterocycloalkyl, $-C(=O)OR_8$, $-OC(=O)R_8$, $-C(=O)NR_8R_9$, $-C(=O)NR_8OR_9$, $-SO_2NR_8R_9$, $-NR_8SO_2R_9$, $-CN$, $-NO_2$, $-NR_8R_9$, $-NR_8C(=O)R_9$, $-NR_8C(=O)(CH_2)_bOR_9$, $-NR_8C(=O)(CH_2)_bR_9$, $-O(CH_2)_bNR_8R_9$, or heterocycle fused to phenyl;

R_4 is alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, each being optionally substituted with one to four substituents independently selected from R_3, or R_4 is halogen or hydroxy;

R_5, R_6 and R_7 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl, wherein each of R_5, R_6 and R_7 are optionally substituted with one to four substituents independently selected from R_3; and

R_8 and R_9 are the same or different and at each occurrence independently hydrogen, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl, or R_8 and R_9 taken together with the atom or atoms to which they are bonded form a heterocycle, wherein each of R_8, R_9, and R_8 and R_9 taken together to form a heterocycle are optionally substituted with one to four substituents independently selected from R_3.

In one embodiment R_2 is $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$.

In one embodiment, $-A-R_1$ is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein *b* is 2 or 3 and wherein R_8 and R_9 are defined above.

In another embodiment, R_2 is $-R_4$, $-(CH_2)_bC(=O)R_5$, $-(CH_2)_bC(=O)OR_5$, $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bC(=O)NR_5(CH_2)_cC(=O)R_6$, $-(CH_2)_bNR_5C(=O)R_6$, $-(CH_2)_bNR_5C(=O)NR_6R_7$, $-(CH_2)_bNR_5R_6$, $-(CH_2)_bOR_5$, $-(CH_2)_bSO_dR_5$ or $-(CH_2)_bSO_2NR_5R_6$, and *b* is an integer ranging from 0-4.

In another embodiment, R_2 is $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bNR_5C(=O)R_6$, 3-triazolyl or 5-tetrazolyl, wherein *b* is 0 and wherein R_8 and R_9 are defined above.

In a preferred embodiment, R_2 is 3-triazolyl or 5-tetrazolyl.

In another preferred embodiment:

(a) $-A-R_1$ is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein *b* is 2 or 3; and

(b) R_2 is $-(CH_2)_bC(=O)NR_5R_6$, $-(CH_2)_bNR_5C(=O)R_6$, 3-triazolyl or 5-tetrazolyl, wherein *b* is 0 and wherein R_8 and R_9 are defined above.

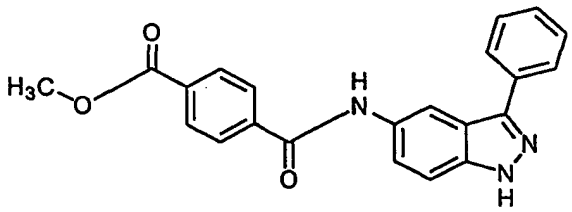
In a more preferred embodiment:

(a) $-A-R_1$ is phenyl, optionally substituted with one to four substituents independently selected from halogen, alkoxy, $-NR_8C(=O)R_9$, $-C(=O)NR_8R_9$, and $-O(CH_2)_bNR_8R_9$, wherein *b* is 2 or 3; and

(b) R_2 is 3-triazolyl or 5-tetrazolyl.

EXAMPLE 15

SYNTHESIS OF METHYL 4-[N-(3-PHENYL-1H-INDAZOL-5-YL) CARBAMOYL]BENZOATE



A. Methyl 4-[N-(1 -acetyl-3-phenyl-1H-indazol-5-yl)carbamoyl]benzoate

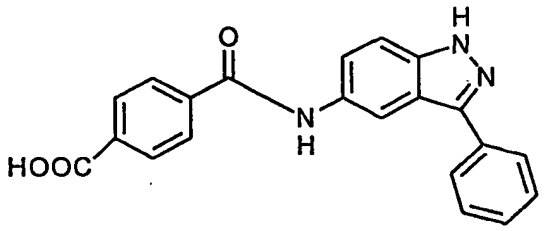
To a flask containing 1-acetyl-5-amino-3-phenyl-1H-indazole (300 mg, 1.2 mmol) was added dichloromethane (10 mL), 4-(dimethylamino)pyridine (75 mg, 0.6 mmol) and triethylamine (180 mg, 1.8 mmol). The mixture was allowed to stir for ten minutes. Terephthalic acid monomethyl ester hydrochloride (285 mg, 1.44 mmol) was then added and stirring continued for 18 hours. The mixture was quenched with 5% sodium bicarbonate and extracted with dichloromethane. The extracts were dried using sodium sulfate, filtered and condensed to give a solid. The solid was recrystallized in ethanol to give the title compound (368 mg, 75% yield). ES-MS (m/z) 414 $[M+1]^+$.

B. Methyl 4-[N-(3-phenyl-1H-indazol-5-yl)carbamoyl]benzoate.

Methyl 4-[N-(3-phenyl-1H-indazol-5-yl)carbamoyl] benzoate (368 mg, 0.890 mmol) was added to a solution of 0.3% ammonia in methanol (18 mL). The mixture was allowed to stir at 70°C for 3 hours. The resulting precipitate was filtered and dried under vacuum to give the title compound (282 mg, 85% yield). ^{1}H NMR (DMSO-d_6) δ 13.22 (br s, 1H), 10.50 (s, 1H), 8.55 (s, 1H), 8.09 (s, 4H), 7.91 (d, 2H), 7.75 (d, 1H), 7.52 (m, 3H), 7.39 (m, 1H), 3.88 (s, 3H); ES-MS (m/z) 372 $[M+1]^+$.

EXAMPLE 16

SYNTHESIS OF 4-[N-(3-PHENYL-1H-INDAZOL-5-YL)CARBAMOYL]BENZOIC ACID

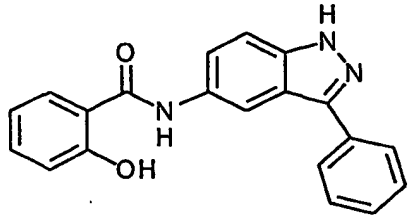


A. 4-[N-(3-phenyl-1H-indazol-5-yl)carbamoyl]benzoic acid

Methyl 4-[N-(3-phenyl-1H-indazole-5-yl)carbamoyl]benzoate (92 mg, 0.247 mmol) was added to a solution of lithium hydroxide (10 mg, 1.23 mmol) in tetrahydrofuran (5 mL) and water (5 mL). The solution was allowed to stir at room temperature for 3 hours. The solution was acidified using a 5% HCl solution. The resulting white precipitate was filtered and dried to provide the title compound (62 mg, 70% yield). ^{1}H NMR (DMSO-d_6) δ 13.22 (br s, 1H), 10.48 (s, 1H), 8.55 (s, 1H), 8.06 (s, 4H), 7.92 (d, 2H), 7.75 (d, 1H), 7.55 (m, 3H), 7.38 (m, 1H); ES-MS (m/z) 358 $[M+1]^+$.

EXAMPLE 17

SYNTHESIS OF (2-HYDROXYPHENYL)-N-(3-PHENYL(1H-INDAZOL-5-YL)CARBOXAMIDE



A. 2-[N-(1-acetyl-3-phenyl-1H-indazole-5-yl)carbamoyl]phenyl acetate and N-(1-acetyl-3-phenyl-1H-indazole-5-yl)acetamide.

To a solution of 5-amino-3-phenylindazole (330 mg, 1.31 mmol) in dichloromethane (11 mL) was added triethylamine (200 mg) and 4-(dimethylamine)pyridine (79 mg, 0.65 mmol). The solution was allowed to stir for fifteen minutes, then acetyl salicyloyl chloride (311 mg, 1.57 mmol) was added. Stirring under nitrogen continued for 18 hours. The solution was then neutralized using 5% sodium bicarbonate solution and

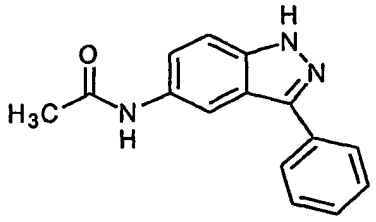
extracted with ethyl acetate. The organic layer was dried with sodium sulfate, filtered and concentrated to give a solid which was purified by chromatography (SiO_2, 25-45% ethyl acetate/ hexanes, respectively). The resulting two fractions provided the title compounds. First fraction: ^{1}H NMR (DMSO-d_6) δ 10.62 (s, 1H), 8.54 (s, 1H), 8.33 (d, 2H), 7.94 (m, 3H), 7.61 (m, 5H), 7.39 (m, 1H), 7.24 (d, 1H), 2.76 (s, 3H), 2.16 (s, 3H); ES-MS (m/z) 414 $[M+1]^+$. Second fraction: ^{1}H NMR (DMSO-d_6) δ 10.23 (s, 1H), 8.47 (s, 1H), 8.29 (d, 1H), 7.93 (d, 2H), 7.73 (d, IH), 7.60 (m, 3H), 2.74 (s, 3H), 2.05 (s, 3H). ES-MS (m/z) 252 $[M+1]^+$.

B. (2-hydroxyphenyl)-N-(3-phenyl(1H-indazole-5-yl))carboxamide.

A solution of 2-[N-(1 -acetyl-3-phenyl-1H-indazole-5-yl)carbamoyl]phenyl acetate (100 mg, 0.241 mmol) in methanol (11 mL) with 0.3% ammonia was allowed to stir for three hours at reflux temperature. The mixture was then acidified with 5% HCl solution until neutral pH. The resulting solid was filtered, dried and triturated with hexanes to give the title compound (45 mg, 57% yield). ^{1}H NMR (DMSO-d_6) δ 13.23 (br s, 1H), 11.92 (br s, 1H), 10.47 (s, 1H), 8.45 (s, 1H), 7.96 (m, 3H), 7.51 (m, 6H), 6.95 (d, 2H); ES-MS (m/z) 330 $[M+1]^+$.

EXAMPLE 18

SYNTHESIS OF N-(3-(PHENYL-1H-INDAZOLE-5-YL))ACETAMIDE



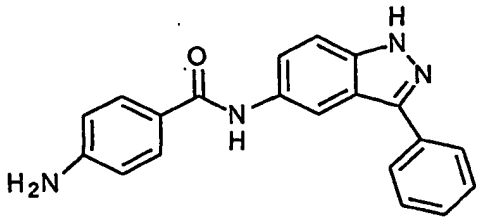
A. 3 -(phenyl-1H-indazole-5-yl)acetamide

N-(1-acetyl-3phenyl-1H-indazole-5-yl)acetamide (70 mg, 0.238 mmol) was added to 0.3% ammonia in methanol (10 mL). The solution was heated at 70°C for 3 hours. The solution was then neutralized using 5% HCl solution. The solution was concentrated and extracted with ethyl acetate. The organics were dried using sodium sulfate, filtered and concentrated to give a white solid. The solid was triturated with diethyl ether and dried under vacuum to give the title compound (35 mg, 59% yield). ^{1}H NMR (DMSO-d_6) δ 13.13

(br s, 1H), 9.97 (s, 1H), 8.37 (s, 1H), 7.87 (d, 2H), 7.48 (br s, 4H), 7.36 (t, 1H), 2.03 (s, 3H); ES-MS (m/z) 252 $[M+1]^+$.

EXAMPLE 19

SYNTHESIS OF (4-AMINOPHENYL)-N-(3-PHENYL(1H-INDAZOL-5-YL))CARLBOXAMIDE



A. N-(1-acetyl-3-phenyl(1H-indazol-5-yl))(4-nitrophenyl)carboxamide

To suspension of 1-acetyl-5-amino-3-phenyl-1H-indazole (250 mg, 1.0 mmol) in dichloromethane (10 mL) was added 4-(dimethylamino)pyridine (60 mg, 0.5 mmol) followed by triethylamine (150 mg, 1.5 mmol). The mixture was allowed to stir for fifteen minutes, then para-nitrobenzoyl chloride (222 mg, 1.2 mmol) was added. The reaction mixture was allowed to stir for 18 hours under nitrogen conditions. It was quenched with 5% sodium bicarbonate and extracted with dichloromethane. The extracts were dried over sodium sulfate, filtered, and condensed to give a precipitate. The precipitate was triturated using hexanes to provide the title compound (295 mg, 74% yield). ^{1}H NMR (DMSO-d_6) δ 10.83 (s, 1H), 8.63 (s, 1H), 8.38 (m, 3H), 8.20 (d, 2H), 7.99 (m, 3H), 7.60 (m, 3H), 2.76 (s, 3H); ES-MS (m/z) 401 $[M+1]^+$.

B. N-(1-acetyl-3-phenyl(1H-indazol-5-yl))(4-aminophenyl)carboxamide

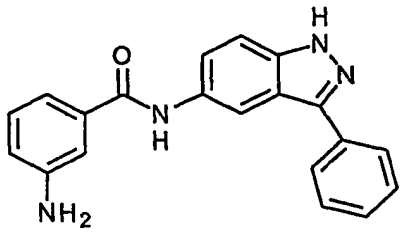
A suspension of N-(1-acetyl-3-phenyl(1H-indazol-5-yl))(4-nitrophenyl)carboxamide (246 mg, 0.710 mmol) and palladium on activated carbon (10%, 57 mg) in ethyl acetate (30 mL) was stirred under hydrogen atmosphere at room temperature for 18 hours. The reaction mixture was filtered through celite and combined with ethyl acetate washings. The filtrate was concentrated to give the title compound (246 mg, 94% yield). ^{1}H NMR (DMSO-d_6) δ 10.04 (s, 1H), 8.61 (s, 1H) 8.31 (d, 1H), 7.99 (m, 2H), 7.64 (m, 4H), 6.58 (d, 2H), 5.78 (s, 2H), 2.76 (s, 3H); ES-MS (m/z) 371 $[M+1]^+$.

C. (4-aminophenyl)-N-(3-phenyl(1H-indazol-5-yl)carboxamide

To a solution of N-(1-acetyl-3-phenyl(1H-indazol-5-yl))(4-aminophenyl)carboxamide (200 mg, 0.664 mmol) in 0.3% ammonia in methanol (12 mL). After the reaction mixture was stirred at room temperature for 3 hours, the mixture was acidified with 5% HCl. The resulting precipitate was filtered and dried to give the title compound (200 mg, 92% yield). ^{1}H NMR (DMSO-d_6) δ 13.14 (br s, 1H), 9.84 (s, 1H), 8.52 (s, 1H), 7.95 (d, 2H), 7.75 (m, 3H), 7.54 (m, 3H), 7.39 (t, 1H), 5.74 (br, 2H); ES-MS (m/z) 329 $[M+1]^+$.

EXAMPLE 20

SYNTHESIS OF (3-AMINOPHENYL)-N-(3-PHENYL(1H-INDAZOL-5-YL))CARBOXAMIDE



A. N-(1-acetyl-3-phenyl(1H-indazol-5-yl))(3-nitrophenyl)carboxamide

The title compound was prepared as described in Example 19 A, using 3-nitrobenzoylchloride (222 mg, 1.20 mmol) (257 mg, 65% yield). ^{1}H NMR (DMSO-d_6) δ 10.85 (s, 1H), 8.82 (s, 1H), 8.63 (s, 1H), 8.41 (m, 3H), 8.00 (m, 3H), 7.84 (t, 1H), 7.60 (m, 3H), 2.77 (s, 3H); ES-MS (m/z) 401 $[M+1]^+$.

B. N-(1-acetyl-3-phenyl(1H-indazol-5-yl))(4-aminophenyl)carboxamide

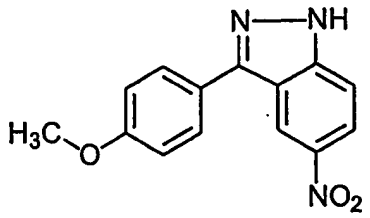
The title compound was prepared as described in Example 19 B (200 mg, 92% yield). ^{1}H NMR (DMSO-d_6) δ 10.36 (s, 1H), 8.63 (s, 1H), 8.34 (d, 1H), 8.00 (m, 3H), 7.60 (m, 3H), 7.12 (m, 3H), 6.74 (d, 1H), 5.32 (s, 2H), 2.77 (s, 3H); ES-MS (m/z) 371 $[M+1]^+$.

C. (3-aminophenyl)-N-(3-phenyl(1H-indazol-5-yl)carboxamide

The title compound was prepared as described in Example 19 C (172 mg, 88% yield). ^{1}H NMR (DMSO-d_6) δ 13.18 (br s, 1H), 10.14 (s, 1H), 8.54 (s, 1H), 7.93 (d, 2H), 7.76 (d, 1H), 7.53 (m, 3H), 7.39 (t, 1H), 7.11 (m, 3H), 6.73 (d, 1H), 5.30 (s, 2H); ES-MS (m/z) 329 $[M+1]^+$.

EXAMPLE 21

SYNTHESIS OF 3-(4-METHOXYPHENYL)-5-NITRO-1H-INDAZOLE



A. 3-Bromo-5-nitro-1H-indazole

The title compound was prepared as described in Example 1 A, using 5-nitro-1H-indazole (9.78 g, 60.0 mmol) (13.674 g, 94% yield): ^{1}H NMR (DMSO-d_6) δ 14.10 (br, 1H), 8.48 (s, 1H), 8.25 (d, 1H), 7.78 (d, 1H); EI-MS (m/z) 243[M+2]$^+$, 241 [M]$^+$.

B. 3-Bromo-1-[2-(methoxyethoxy)methyl-5-nitro-1H-indazole

The title compound was prepared as described in Example 2 A, using 3-bromo-5-nitro-1H-indazole (4.84 g, 20.0 mmol) (4.52 g, 68% yield): mp 74°C; ^{1}H NMR ($CDCl_3$) δ 8.64 (d, 1H), 8.37 (dd, 1H), 7.69 (d, 1H), 5.82 (s, 2H), 3.69 (m, 2H), 3.50 (m, 2H), 3.34 (s, 3H); EI-MS (m/z) 231[M+2]$^+$, 329 [M]$^+$.

C. 1-[2-(Methoxyethoxy)methyl]-3-(4methoxyphenyl)-5-nitro-1H-indazole

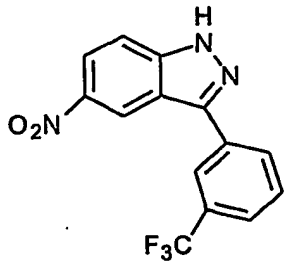
The title compound was prepared as described in Example 2 B, using 3-bromo-1-[2-(methoxyethoxy)methyl]-5-nitro-1H-indazole (0.66 g, 2.0 mmol) and 4-methoxyphenylboronic acid (0.456 g, 3.0 mmol) (0.584 g, 82% yield): mp 65 °C; ^{1}H NMR ($CDCl_3$) δ 8.72 (d, 1H), 8.14 (dd, 1H), 7.76 (d, 1H), 7.70 (d, 2H), 7.14 (d, 2H), 5.77 (s, 2H), 3.97 (m, 2H), 3.92 (s, 3H), 3.58 (m, 2H), 3.38 (s, 3H); EI-MS (m/z) 357 [M]$^+$.

D. 3-(4-Methoxyphenyl)-5-nitro-1H-indazole

A solution of 1-[2-(methoxyethoxy)methyl]-3-(4-methoxyphenyl)-5-nitro-1H-indazole (0.51 g, 1.4 mmol) in methanol (10 mL) and 6 N hydrochloric acid solution (10 mL) was heated at 75°C for 8 hours. After the reaction mixture was cooled to room temperature, a yellow solid was precipitated. It was recrystallized from diethyl ether to provide the title compound (0.270 g, 72% yield): mp 153 °C; ^{1}H NMR ($CDCl_3$) δ 10.42 (br s, 1H), 8.99 (d, 1H), 8.33 (dd, 1H), 7.91 (d, 2H), 7.56 (d, 1H), 7.11 (d, 2H); ES-MS (m/z) 269 [M]$^+$.

EXAMPLE 22

SYNTHESIS OF 5-NITRO-3-[3-(TRIFLUOROMETHYL)PHENYL]-1H-INDAZOLE

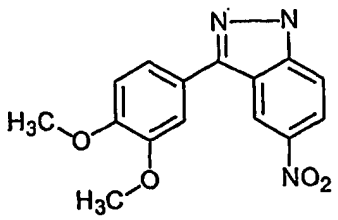


A. 5-Nitro-3-[3-(trifluoromethyl)phenyl]-1H-indazole

The title compound was prepared as described in Example 2 B using 3-trifluoromethylphenyl boronic acid (40 mg, 0.10 mmol) (23 mg, 75% yield). ^{1}H NMR (DMSO-d_6) δ 8.95 (s, 1H), 8.36 (d, 1H), 8.3 (m, 2H), 7.85-7.8 (m, 3H); ES-MS (m/z) 308 [M+1]$^+$.

EXAMPLE 23

SYNTHESIS OF 3-(3,4-DIMETHOXYPHENYL)-5-NITRO-1H-INDAZOLE



A. 3-(3,4-Dimethoxyphenyl)-1-[2-(methoxyethoxy)methyl]-5-nitro-1H-indazole

The title compound was prepared as described in Example 2 B, using 3-bromo-1-[2-(methoxyethoxy)methyl]-5-nitro-1H-indazole (0.50 g, 1.5 mmol) and 3,4-dimethoxyphenylboronic acid (0.40 g, 2.2 mmol) (0.467 g, 80% yield): ^{1}H NMR ($CDCl_3$) δ 8.97 (s, 1H), 8.35 (d, 1H), 7.70 (d, 1H), 7.51 (m, 2H), 7.06 (d, 1H), 5.89 (s, 2H), 4.01 (s, 3H), 4.00 (s, 3H), 3.72 (m, 2H), 3.51 (m, 2H), 3.56 (s, 3H); EI-MS (m/z) 387 [M]$^+$.

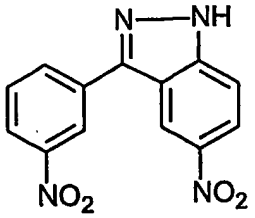
B. 3-(3,4-Dimethoxyphenyl)-5-nitro-1H-indazole

The title compound was prepared as described in Example 21 D, using 3-

(3,4-dimethoxyphenyl)-1-[2-(methoxyethoxy)methyl]-5-nitro-1H-indazole (0.387 g, 1.0 mmol) (0.205 g, 69% yield): mp 172-173 °C; ^{1}H NMR (DMSO-d_6) δ 13.79 (br, 1H), 8.89 (d, 1H), 8.25 (dd, 1H), 7.77 (d, 1H), 7.57 (dd, 1H), 7.51 (s, 1H), 7.17 (d, 1H), 3.88 (s, 3H), 3.85 (s, 3H); ES-MS (m/z) 300 $[M+1]^+$.

EXAMPLE 24

SYNTHESIS OF 5-NITRO-3-(3-NITROPHENYL)-1H-INDAZOLE



A. 1-[2-(Methoxyethoxy)methyl]-5-nitro-3-(3-nitrophenyl)-1H-indazole

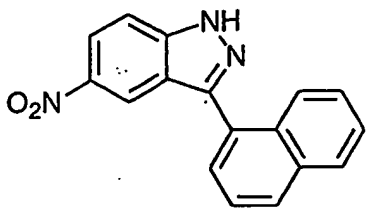
The title compound was prepared as described in Example 2 B, using 3-bromo-1-[2-(methoxyethoxy)methyl]-5-nitro-1H-indazole (0.50 g, 1.5 mmol) and 3-nitrophenylboronic acid (0.376 g, 2.25 mmol) (0.487 g, 87% yield): ^{1}H NMR ($CDCl_3$) δ 8.98 (d, 1H), 8.86 (s, 1H), 8.30-8.42 (m, 3H), 7.77 (m, 2H), 5.94 (s, 2H), 3.74 (m, 2H), 3.54 (m, 2H), 3.36 (s, 3H); EI-MS (m/z) 372 $[M]^+$.

B. 5-Nitro-3-(3-nitrophenyl)-1H-indazole

The title compound was prepared as described in Example 21 D, using 1-[2-(methoxyethoxy)methyl]-5-nitro-3-(3-nitrophenyl)-1H-indazole (0.42 g, 1.13 mmol) (0.208 g, 65% yield): mp 249-251 °C; ^{1}H NMR (DMSO-d_6) δ 14.00 (br s, 1H), 9.00 (s, 1H), 8.73 (s, 1H), 8.51 (d, 1H), 8.30 (m, 2H), 7.85 (m, 2H); ES-MS (m/z) 285 $[M+1]^+$.

EXAMPLE 25

SYNTHESIS OF 3-NAPHTHYL-5-NITRO-1H-INDAZOLE

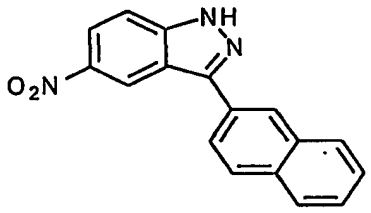


A. 3-Naphthyl-5-nitro-1H-indazole

The title compound was prepared as described in Example 2 B using 1-napthyl boronic acid (117 mg, 0.68 mmol) (90 mg, 46% yield). ^{1}H NMR (DMSO-d_6) δ 14.09 (s, 1H), 8.52 (s, 1H, 8.27 (dd, 2H), 8.11 (t, 2H) 7.86 (t, 2H), 7.73 (t, 1H), 7.6 (m, 2H); ES-MS (m/z) 290 $[M+1]^+$.

EXAMPLE 26

SYNTHESIS OF 3-(2-NAPHTHYL)-5-NITRO-1H-INDAZOLE

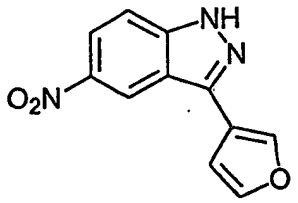


A. 3-(2-Naphthyl)-5-nitro-1H-indazole

The title compound was prepared as described in Example 2 B using 2-napthyl boronic acid (51 mg, 0.68 mmol) (95 mg, 48% yield). ^{1}H NMR (DMSO-d_6) δ 14.01 (s, 1H), 9.11 (s, 1H), 8.62 (s, 1H) 8.30 (d, 1H), 8.0-8.1 (m, 3H), 8.0 (m, 1H), 7.82 (d, 1H), 7.6 (m, 2H); ES-MS (m/z) 290 $[M+1]^+$.

EXAMPLE 27

SYNTHESIS OF 3-(5-NITRO-1H-INDAZOL-3-YL)FURAN

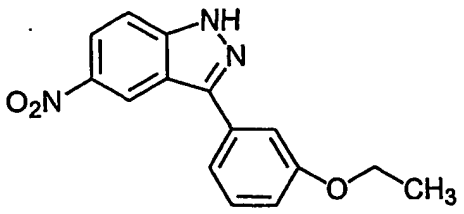


A. 3-(5-Nitro-1H-indazol-3-yl)furan

The title compound was prepared as described in Example 2 B using 3-furan boronic acid (51 mg, 0.45 mmol) (14 mg, 20% yield). HPLC retention time on C18 column, 24.3 min. ES-MS (m/z) 230 $[M+1]^+$.

EXAMPLE 28

SYNTHESIS OF 3-ETHOXY-1-(5-NITRO(1H-INDAZOL-3-YL))BENZENE

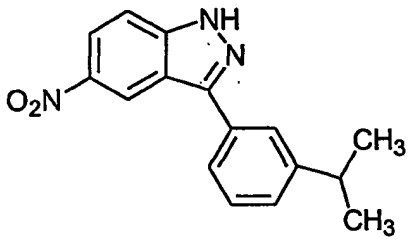


A. 3-Ethoxy-1-(5-nitro(1H-indazol-3-yl))benzene

The title compound was prepared as described in Example 2 B using 3-ethoxyphenyl boronic acid (75 mg, 0.45 mmol) (75 mg, 82% yield). ES-MS (m/z) 284 $[M+1]^+$.

EXAMPLE 29

SYNTHESIS OF 3-[3-(METHYLETHYL)PHENYL]-5-NITRO-1H-INDAZOLE

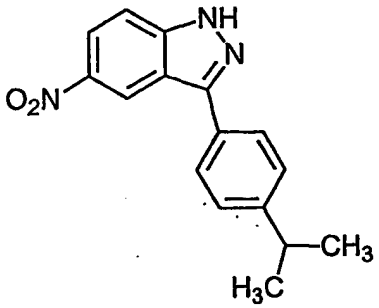


A. 3-[3-(Methylethyl)phenyl]-5-nitro-1H-indazole

The title compound was prepared as described in Example 2 B using 3-isopropylphenyl boronic acid (74 mg, 0.45 mmol) (40 mg, 47% yield). ES-MS (m/z) 282 $[M+1]^+$.

EXAMPLE 30

SYNTHESIS OF 3-[4-(METHYLETHYL)PHENYL]-5-NITRO-1H-INDAZOLE

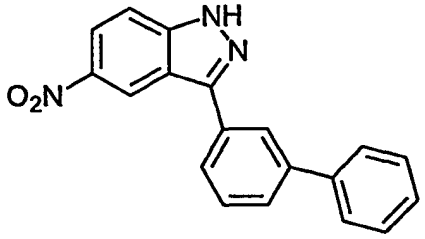


A. 3-[4-(Methylethyl)phenyl]-5-nitro-1H-indazole

The title compound was prepared as described in Example 2 B using 4-isopropylphenyl boronic acid (74 mg, 0.45 mmol) (43 mg, 47% yield). ES-MS (m/z) 282 $[M+1]^+$.

EXAMPLE 31

SYNTHESIS OF 5-NITRO-3-(3-PHENYLPHENYL)-1H-INDAZOLE

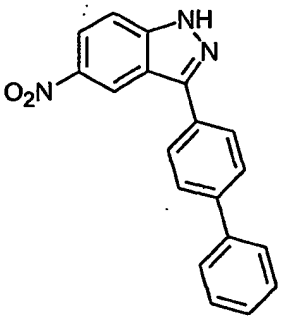


A. 5-Nitro-3-(3-phenylphenyl)-1H-indazole

The title compound was prepared as described in Example 2 B using 3-metabiphenyl boronic acid (89 mg, 0.45 mmol) (50 mg, 53% yield). ES-MS (m/z) 316 $[M+1]^+$.

EXAMPLE 32

SYNTHESIS OF 5-NITRO-3-(4-PHENYLPHENYL)-1H-INDAZOLE

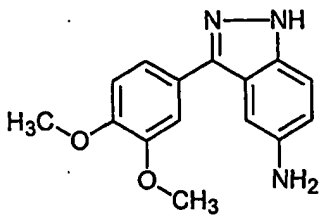


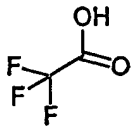
A. 5-Nitro-3-(4-phenylphenyl)-1H-indazole

The title compound was prepared as described in Example 2 B using 3-phenylphenylboronic acid (89 mg, 0.45 mmol) (52 mg, 53% yield). ES-MS (m/z) 316 $[M+1]^+$.

EXAMPLE 33

SYNTHESIS OF 5-AMINO-3-(3,4-DIMETHOXYPHENYL)-1H-INDAZOLE TRIFLOUROACETATE



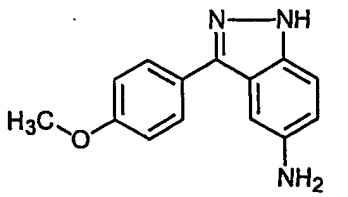


A. 5-Amino-3-(3 ,4-Dimethoxyphenyl)-1H-indazole Trifluoroacetate

A suspension of 3-(3,4-dimethoxyphenyl)-5-nitro-1H-indazole (0.20 g, 0.67 mmol) and palladium (10 wt % on activated carbon, 30 mg) in ethanol (20 mL) with 5 drops of concentrated hydrochloric acid was stirred under hydrogen at ambient temperature for 24 hours. It was filtered with celite and washed with ethanol. The filtrate was concentrated and the residue was purified by preparative HPLC to provide the title compound (0.021 g, 12% yield): mp 150°C (dec.); ^{1}H NMR (DMSO-d_6) δ 13.4 (br s, 1H), 9.8 (br s, 2H), 7.96 (s, 1H), 7.68 (d, 1H), 7.46 (m, 2H), 7.32 (d, 1H), 7.13 (d, 1H), 3.87 (s, 3H), 3.83 (s, 3H); ES-MS (m/z) 270 $[M+1]^+$.

EXAMPLE 34

SYNTHESIS OF 5-AMINO-3-(4-METHOXYPHENYL)-1H-INDAZOLE HYDROCHLORIDE

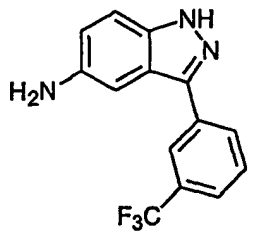


A. 5-Amino-3-(4-methoxyphenyl)-1H-indazole Hydrochloride

The title compound was prepared as described in Example 33 A, using 3-(4-methoxyphenyl)-5-nitro-1H-indazole (0.22 g, 0.8 mmol) (0.121 g, 55% yield): mp 240°C (dec.); ^{1}H NMR (DMSO-d_6) δ 13.0 (br s, 1H), 10.45 (br s, 2H), 8.10 (s, 1H), 7.85 (d, 2H), 7.72 (d, 1H), 7.41 (dd, 1H), 7.13 (d, 2H); ES-MS (m/z) 240 $[M+1]^+$.

EXAMPLE 35

SYNTHESIS OF 3-[3-(TRIFLUOROMETHYL)PHENYL]-1H-INDAZOLE-5-YLAMINE

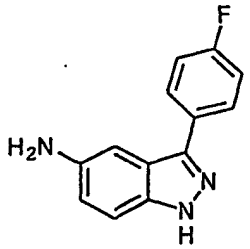


A. 3-[3-(Trifluoromethyl)phenyl]-1H-indazole-5-ylamine

The title compound was prepared as described in Example 36 (15 mg, 5% yield). ^{1}H NMR (DMSO-d_6) δ 13.02 (s, 1H), 8.20 (d, 1H), 8.16 (s, 1H), 7.7-7.68 (m, 2H), 7.34 (d, 1H), 7.11 (s, 1H), 6.86 (d, 1H), 5.0 (br s, 2H); ES-MS (m/z) 278 $[M+1]^+$.

EXAMPLE 36

SYNTHESIS OF 3-(4-FLUROPHENYL)-1H-INDAZOLE-5-YLAMINE



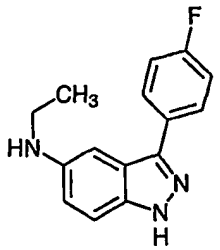
A. 3-(4-Fluorophenyl)-1H-indazole-5-ylamine

To a solution of 1-{[3-(4-fluorophenyl)-5-nitro(1H-indazolyl)]methoxy}-2-methoxyethane (100 mg, 0.29 mmol) in ethanol (30 mL) was added a scoup of Pd/carbon. The reaction was stirred overnight at room temperature under an atmosphere of hydrogen. It was filtered over celite and the solution concentrated to an oil. The oil was taken up in methanol (20 mL) and 6N HCl (20 mL) and the solution was heated to 75°C for 3 hours.

The solution was concentrated under vacuo, added to saturated bicarbonate (100 mL) and extracted with ethyl acetate (3 x 30 mL). The organic layers were dried (Na_2SO_4), concentrated to an oil and chromatographed on silica gel, eluting with 50% ethyl acetate/hexane to give the title compound (35 mg, 53% yield). ^1H NMR ($CDCl_3$) δ 10.1 (br s, 1H), 7.89 (dd, 1H), 7.23-7.16 (m, 4H), 6.91 (dd, 1H), 3.6 (br s, 1H); ES-MS (m/z) 228 $[M+1]^+$.

EXAMPLE 37

SYNTHESIS OF ETHYL[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]AMINE

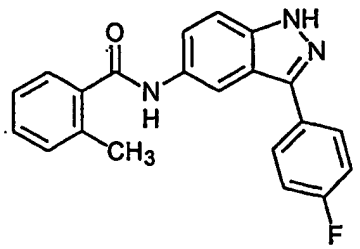


A. Ethyl[3-(4-fluorophenyl)(1 H-indazol-5-yl)]amine

To a solution of 1-{[3-(4-fluorophenyl)-5-nitro(1H-indazolyl)]methoxy}-2-methoxyethane (100 mg, 0.29 mmol) in ethanol (30 mL, containing a contaminant of acetaldehyde) was added a scoup of Pd/carbon. The reaction was stirred overnight at room temperature under an atmosphere of hydrogen. It was filtered over celite and the solution concentrated to an oil. The oil was taken up in methanol (20 mL) and 6N HCl (20 mL) and heated to 75°C for 3 hours. The solution was concentrated under vacuo, added to saturated bicarbonate (100 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layers were dried (Na_2SO_4), concentrated to an oil and chromatographed on silica gel, eluting with 50% ethyl acetate/hexane to give the title compound (8 mg, 11% yield). ^1H NMR ($CDCl_3$) δ 10.4 (br s, 1H), 7.91 (dd, 2H), 7.26-7.17 (m, 3H), 6.99 (s, 1H), 6.84 (dd, 1H), 3.21 (q, 2H), 1.31 (t, 3H); ES-MS (m/z) 256 $[M+1]^+$.

EXAMPLE 38

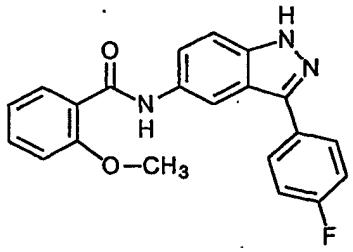
SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)] (2-METHYLPHENYL)CARBOXAMIDE



To a solution of 1-{[3-(4-fluorophenyl)-5-amino(1H-indazolyl)]methoxy}-2-methoxyethane (100 mg, 0.32 mmol) in pyridine (3 mL) was added benzoyl chloride (45 µL, 0.38 mmol). The solution was stirred for 12 hours when water (80 mL) was added and the solid filtered. The solid was then taken up in methanol (3 mL) and 6N HCl (3 mL) and heated to 80°C for 3 hours. Water (80 mL) was then added and the solid filtered and dried to give the title compound (20 mg, 19% yield). ^{1}H NMR (DMSO-d_6) 6 13.3 (br s, 1H), 10.37 (s, 1H), 8.57 (s, 1H), 8.0-7.9 (m, 5H), 7.78 (d, 1H), 7.6-7.5 (m, 4H), 7.40 (t, 2H); ES-MS (m/z) 332 $[M+1]^+$.

EXAMPLE 39

SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)](2-METHOXYPHENYL)CARBOXAMIDE

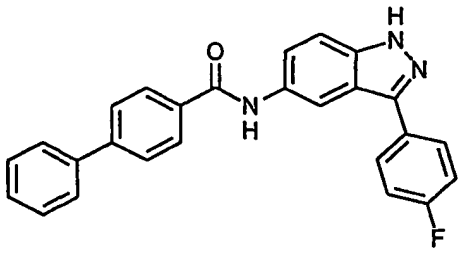


A. N-[3-(4-Fluorophenyl)(1H-indazol-5-yl)](2-methoxyphenyl)carboxamide

The title compound was prepared as described in Example 38 using 2-methoxybenzoyl chloride (73 µL, 0.45 mmol) (45 mg, 39% yield). ^{1}H NMR (DMSO-d_6) δ 13.2 (br s, 1H), 10.35 (s, 1H), 8.55 (s, 1H), 7.98 (dd, 2H), 7.78 (d, 1H), 7.58 (d, 2H), 7.54 (s, 1H), 7.46 (t, 1H), 7.39 (t, 2H), 7.16 (dd, 1H), 3.85 (s, 3H); ES-MS (m/z) 362 $[M+1]^+$.

EXAMPLE 40

SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)](4-PHENYLPHENYL)CARBOXAMIDE

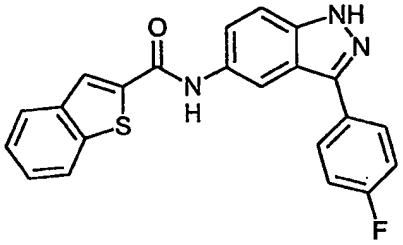


A. N-[3-(4-Fluorophenyl)(1H-indazol-5-yl)](4-phenylphenyl)carboxamide

The title compound was prepared as described in Example 38 using 4-phenylbenzoyl chloride (83 mg, 0.45 mmol) (55 mg, 42% yield). ^{1}H NMR (DMSO-d_6) δ 13.3 (br s, 1H), 10.41 (s, 1H), 8.59 (s, 1H), 8.11 (d, 2H), 7.99 (dd, 2H), 7.8 (m, 3H), 7.77 (d, 3H), 7.60 (d, 1H), 7.52 (t, 2H), 7.44 (d, 1H), 7.39 (d, 1H); ES-MS (m/z) 408 $[M+1]^+$.

EXAMPLE 41

SYNTHESIS OF BENZO[B]THIOPHEN-2-YL-N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]CARBOXAMIDE

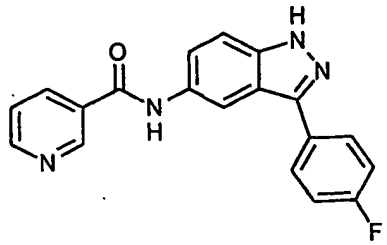


A. Benzor[b]thiophen-2-yl-N-[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide

The title compound was prepared as described in Example 38 using 2-thiophenecarbonyl chloride (75 mg, 0.45 mmol) (48 mg, 39% yield). ^{1}H NMR (DMSO-d_6) δ 13.3 (br s, 1H), 10.66 (s, 1H), 8.55 (s, 1H), 8.41 (s, 1H), 8.1-7.9 (m, 4H), 7.80 (d, 1H), 7.63 (d, 1H), 7.50 (m, 2H), 7.41 (t, 2H); ES-MS (m/z) 388 $[M+1]^+$.

EXAMPLE 62

SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-3-PYRIDYLCARBOXAMIDE

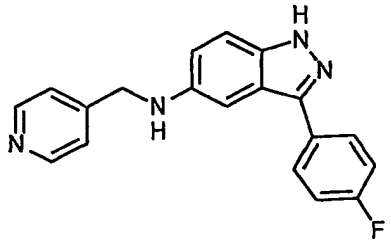


A. N-[3-(4-Fluorophenyl)(1H-indazol-5-yl)]-3-pyridylcarboxamide

The title compound was prepared as described in Example 55 A using pyridine-3-carbonyl chloride hydrochloride (152 mg, 0.86 mmol) (29 mg, 10% yield).). ^{1}H NMR ($CDCl_3$) δ 13.28 (s, 1H), 10.55 (s, 1H), 9.17 (s, 1H), 8.78 (d, 1H), 8.57 (s, 1H), 8.34 (d, 1H), 7.99 (dd, 2H), 7.78 (d, 1H), 7.63-7.57 (m, 2H), 7.40 (t, 2H); ES-MS (m/z) 333 $[M+ 1]^+$.

EXAMPLE 63

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)](4-PYRIDYLMETHYL)AMINE



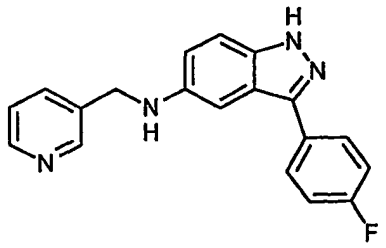
A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)(4-pyridylmethyl)amine

To a solution of N-[3-(4-fluorophenyl)(1H-indazol-5-yl)]-4-pyridylcarboxamide (50 mg, 0.12 mmol) in THF (3 mL) was added lithium aluminum hydride (LAH) (9 mg, 0.24 mmol). The solution was stirred for 3 hours when an additional equivalence of LAH was added. The reaction was stirred for another 3 hours when it was quenched with ethyl acetate and water (100 mL) was added. The layers were separated and the water layer extracted with ethyl acetate (3x30 mL). The combined organic layers were

dried (Na_2SO_4) and concentrated to an oil. The oil was taken up in methanol (10 mL) and 6N HCl (10 mL) and heated to 80°C for 2 hours when it was quenched with $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated to afford the title compound (7.5 mg, 20% yield). ^1H NMR ($CDCl_3$) δ 8.6 (br s, 1H), 7.76 (dd, 2H), 7.35 (d, 2H), 7.24 (d, 2H), 7.15 (t, 2H), 6.9-6.8 (m, 2H), 4.43 (s, 2H); ES-MS (m/z) 319$[M+1]^+$.

EXAMPLE 64

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)](3-PYRIDYLMETHYL)AMINE

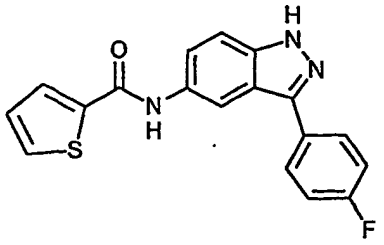


A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)](3-pyridylmethyl)amine

The title compound was prepared as described in Example 63 A using N-[3-(4-fluorophenyl)(1H-indazol-5-yl)]-3-pyridylcarboxamide (126 mg, 0.3 mmol) (8 mg, 8% yield). ^1H NMR ($CDCl_3$) δ 12.87 (s, 1H), 8.66 (s, 1H), 8.45 (s, 1H), 8.85 (m, 3H), 8.39-8.27 (m, 3H), 6.95 (d, 1H), 6.91 (s, 1H), 6.18 (t, 1H), 4.37 (d, 2H); ES-MS (m/z) 319 $[M+1]^+$.

EXAMPLE 65

SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-2-THIENYLCARBOXAMIDE

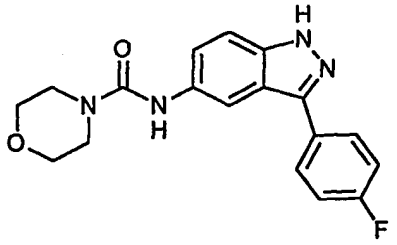


A. N-[3-(4-Fluorophenyl)(1H-indazol-5-yl)]-2-thienylcarboxamide

The title compound was prepared as described in Example 55 A using 2-thiophenecarbonyl chloride (51 µg, 0.47 mmol) (25 mg, 16% yield). ^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1H), 8.48 (s, 1H), 8.08 (d, 1H), 7.9 (m, 2H) 7.85 (d, 1H), 7.74 (d, 1H), 7.59 (d, 1H), 7.38 (t, 2H), 7.23 (t, 1H); ES-MS (m/z) 338 $[M+1]^+$.

EXAMPLE 66

SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]MORPHOLIN-4-YLCARBOXAMIDE

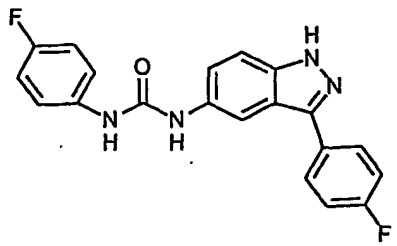


A. N-[3-(4-Fluorophenyl)(1H-indazol-5-yl)]morpholin-4-ylcarboxamide

The title compound was prepared as described in Example 55 A using morpholine-4-carbonyl chloride (45 µL, 0.38 mmol) (20 mg, 19% yield). ^{1}H NMR (DMSO-d_6) δ 13.1 (s, 1H), 8.60 (s, 1H), 8.13 (s, 1H), 7.94 (dd, 2H), 7.49 (s, 2H), 7.37 (t, 2H), 3.63 (m, 4H), 3.43 (m, 4H); ES-MS (m/z) 341 $[M+1]^+$.

EXAMPLE 67

SYNTHESIS OF N-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)][(4-FLUOROPHENYL)AMINO]CARBOXAMIDE



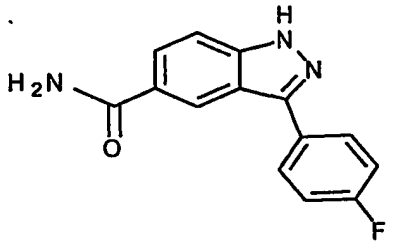
A. N-[3-(4-fluorophenyl)(1H-indazol-5-yl)][(4-fluorophenyl)amino]carboxamide

To a solution of 3-(4-fluorophenyl)-1-(2-methoxyethoxy)-1H-indazole-5-ylamine (115 mg, 0.36 mmol) in dioxane (5 mL) was added 4-fluorophenyl isocyanate (50 µL, 0.44 mmol). The reaction was stirred overnight at room temperature. It was then filtered and the solid dried in a vaxuum oven. The solid was then taken up in 6N HCl (10

mL) and methanol (10 mL) and heated to 80°C for 2 hours. The reaction was then cooled to room temperature and quenched with $NaHCO_3$ (100 mL) and extracted with ethyl acetate (3x40 mL). The organic layers were combined and dried with magnesium sulfate ($MgSO_4$) and concentrated to a solid to afford the title compound (25 mg, 19% yield). 1H NMR ($CDCl_3$) δ 13.1 (br s, 1H), 9.32 (s, 2H), 8.28 (s, 1H), 7.94 (dd, 2H), 7.52 (d, 1H), 7.48 (dd, 2H), 7.38 (t, 2H), 7.33 (dd, 1H), 7.11 (t, 2H); ES-MS (m/z) 364 $[M+1]^+$.

EXAMPLE 68

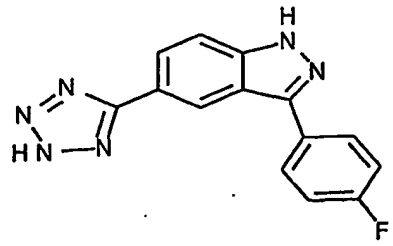
SYNTHESIS OF 3-(4-FLUOROPHENYL)-1H-INDAZOLE-5-CARBOXAMIDE



To a solution of 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (200 mg, 0.63 mmol) in methylene chloride (20 mL) was added saturated ammonium hydroxide (NH_4OH). The solution was stirred overnight at room temperature when it was added to water (100 mL) and extracted with ethyl acetate (3x40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuo to an oil. The resulting oil was chromatographed on silica gel, eluting with 10% methanol in methylene chloride to give the title compound (115 mg, 72%). ^1H NMR (DMSO-d_6) δ 13.4 (s, 1H), 8.60 (s, 1H), 8.09 (m, 2H), 7.94 (d, 1H), 7.61 (d, 1H), 7.38 (t, 2H); ES-MS (m/z) 256 $[M+1]^+$.

EXAMPLE 69

SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-2H-1,2,3,4-TETRAZOLE

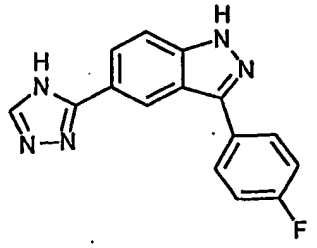


A. 5-[3-(4-Fluorophenyl)-1H-indazol-5-yl]-2H-1,2,3,4-tetrazole

The title compound was prepared as described in Example 73 B. To a solution of the nitrite (300 mg, 1.26 mmol) in toluene (10 mL) was added the azidotributyltin (380 μL, 1.32 mmol). The reaction was then heated to reflux overnight. The solid was isolated by filtration, taken up in a 1:1 solution of THF:concentrated HCl and stirred at room temperature for 4 hours. The product was then extracted with ethyl acetate/water, dried (Na_2SO_4), and chromatographed on silica gel eluting with 15% methanol in methylene chloride to give the title tetrazole (80 mg, 23% yield). ^{1}H NMR (DMSO-d_6) δ 13.6 (s, 1H), 8.77 (s, 1H) 8.08-8.13 (m, 3H), 7.83 (d, 1H), 7.45 (t, 2H); ES-MS (m/z) 281 $[M+1]^+$.

EXAMPLE 70

SYNTHESIS OF 3-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-1H-1,2,4-TRIAZOLE

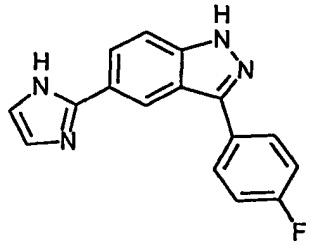


A. 3-[3-(4-Fluorophenyl)-1H-indazol-5-yl]-1H-1,2,4-triazole

The title compound was prepared as described in Example 68. The amide (350 mg, 1.2 mmol) was heated in DMF acetal (40 mL) at 90°C for 4 hrs. The solvent was then removed under vacuo to give an oil which was taken up in a solution of hydrazine (0.5 mL) in acetic acid (40 mL). The subsequent solution was stirred at room temperature overnight. Water was then added to the reaction and the resulting solid filtered then dried in a vacuum oven. The product was purified by silica gel column chromatography eluting with 15% methanol in methylene chloride to give the title triazole (190 mg, 57% yield). ^{1}H NMR (DMSO-d_6) δ 13.4 (br s, lH), 8.67 (s, 1H), 8.4 (br s, 1H), 8.12-8.03 (m, 3H), 7.71 (d, lH), 7.41 (dt, 2H); ES-MS (m/z) 280 $[M+l]^+$.

EXAMPLE 71

SYNTHESIS OF 3-(4-FLUOROPHENYL)-5-IMIDAZOL-2-YL-1H-INDAZOLE

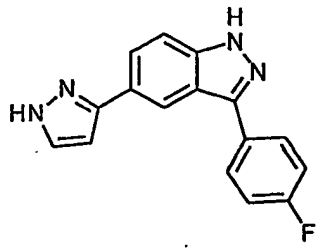


A. 3-(4-Fluorophenyl)-5-imidazol-2-yl-1H-indazole

To a solution of the nitrile (100 mg, 0.31 mmol) in methanol (60 mL) was bubbled in gaseous hydrochloric acid at 0 °C. The reaction was stirred at room temperature overnight when it was rotary evaporated to a solid and washed with ether (20 mL). Methanol (60 mL) was added followed by 1-amino-2,2-dimethoxyethane (0.5 mL, excess) and the reaction heated to a gentle reflux overnight. The reaction was then concentrated under vacuo to an oil when H_2SO_4 (30 mL) was added. The reaction was stirred at room temperature for 4 hrs when it was added to ice and neutralized with potassium carbonate (K_2CO_3). The aqueous layer was then extracted with ethyl acetate and the subsequent organic layer dried (Na_2SO_4) and concentrated to an oil. The product was isolated by column chromatography on silica gel eluting with 5% methanol in methylene chloride to give the imidazole (50 mg, 58% yield). ^{1}H NMR (DMSO-d_6) δ 13.4 (s, 1H), 8.58 (s, 1H), 8.11-8.06 (m, 3H), 7.65 (d, 1H), 7.40 (t, 2H), 7.16 (s, 1H); ES-MS (m/z) 279 $[M+1]^+$.

EXAMPLE 72

SYNTHESIS OF 3-(4-FLUOROPHENYL)-5-PYRAZOL-3-YL-1H-INDAZOLE

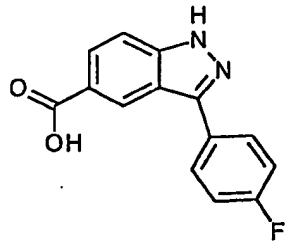


A. 3-(4-Fluorophenyl)-5-pyrazol-3-yl-1H-indazole

To a solution of 3-(4-fluorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (265 mg, 0.82 mmol) in THF (10 mL) at -78°C was added methyl lithium (1.2 mL of a 1.0 molar solution in THF, 1.2 mmol). The solution was allowed to warm to room temperature over 3 hours when it was worked up with ethyl acetate/water, dried (Na_2SO_4), and concentrated under vacuo to give the methyl ketone. The product was then taken up in DMF dimethoxy acetal (30 mL) and heated to 90°C overnight. The solvent was then removed under vacuo and a solution of hydrazine (1 mL) in acetic acid (40 mL) was added. After stirring at room temperature overnight, the acetic acid was removed under vacuo and the solution neutralized with aqueous $NaHCO_3$, extracted with ethyl acetate, dried (Na_2SO_4), and concentrated to an oil. The THP-protected indazole was then isolated after silica gel column chromatography eluting with 40% ethyl acetate in hexane. The solid was taken up in 6N HCl (30 mL) and methanol (30 mL) and stirred at room temperature for 1 hour when the methanol was removed under vacuo and the resulting solution extracted with ethyl acetate/water. The organic layer was then dried (Na_2SO_4) and the product isolated after silica gel column chromatography eluting with 50% ethyl acetate in hexane to give the title pyrazole (40 mg, 17% yield). ^1H NMR (DMSO-d_6) δ 13.3 (m, 2H), 12.8 (br s, 1H), 8.4 (br s, 1H), 8.08 (m, 2H), 7.95 (d, 1H), 7.8 (br s, 1H), 7.6 (m, 1H), 7.39 (t, 2H), 6.8 (br s, 1H); ES-MS (m/z) 279 $[M+1]^+$.

EXAMPLE 73

SYNTHESIS OF 3-(4-FLUOROPHENYL)-1H-INDAZOLE-5-CARBOXYLIC ACID



A. 4-Fluoro-3-{(4-fluorophenyl)carbonyl}benzenecarbonitrile

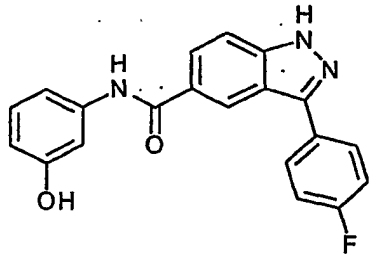
To a flask containing 4-fluorobenzonitrile (10 g, 0.08 mol) dried under vacuum and placed under nitrogen was added anhydrous tetrahydrofuran (200 mL). The flask was placed in a dry ice/acetone bath and cooled to -78 °C. A 2 molar solution of

A. tert-Butyl 3-{[3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino)propanoate

To a suspension of 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid (200 mg, 0.780 mmol) in dimethyl formamide (10mL) was added 1-Hydroxybenzotriazole (126 mg, 0.936 mmol) and 4-(dimethylamino)pyridine (114 mg, 0.936 mmol). The mixture was allowed to stir for fifteen minutes. 1-ethyl-(3-dimethylamino)carbodiimide hydrochloride (179 mg, 0.936 mmol) was then added and stirring continued for fifteen additional minutes. H-β-ala-*O-t-Bu*-hydrochloride (170 mg, 0.936 mmol) was added and stirring continued at ambient temperature for 18 hours. The mixture was condensed and extracted with 5% sodium bicarbonate and ethyl acetate. The extracts were dried over sodium sulfate, filtered, and concentrated to afford the title compound (165 mg, 55%). ^{1}H NMR (DMSO-d_6) δ 13.43 (s, 1H), 8.65 (s, 1H), 8.47 (s, 1H), 8.02 (m, 2H), 7.85 (d, 2H), 7.59 (d, 1H), 7.36 (m, 2H), 3.46 (q, 4H), 1.37 (s, 9H); ES-MS (m/z) 384 $[M+1]^+$.

EXAMPLE 87

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-(3-HYDROXYPHENYL)CARBOXAMIDE

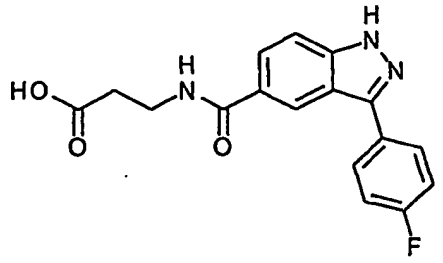


A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)]-N-(3-hydroxyphenyl)carboxamide

The title compound was prepared as described in Example 86 A, using 3-aminophenol (93.6 mg, 0.858 mmol) to provide the title compound (88 mg, 32%). ^{1}H NMR (DMSO-d_6) δ 13.49 (br s, 1H), 10.19 (s, 1H), 9.38 (s, 1H), 8.60 (s, 1H), 8.08 (d, 2H), 7.93 (d, 1H), 7.65 (d, 1H), 7.38 (m, 3H), 7.12 (m, 2H), 6.49 (d, 1H); ES-MS (m/z) 348 $[M+1]^+$.

EXAMPLE 88

SYNTHESIS OF 3-{[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO)PROPANOIC ACID

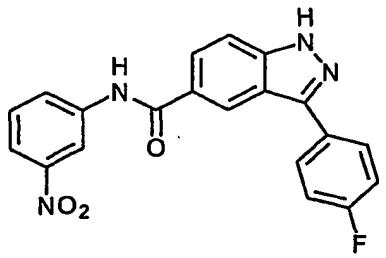


A. 3-{[3-(4-Fluorophenyl)-1H-indazol-5-yl]carbonylamino)propanoic acid

To a solution containing Example 86 (150 mg, 0.391 mmol) in dioxane (2 mL) was added 6N HCl (2 mL). The reaction mixture was allowed to stir at ambient temperature for 18 hours. The solution was quenched with water (30 mL) and the mixture extracted with ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to give a solid. The solid was triturated with dichloromethane and hexanes to provide the title compound (94 mg, 73%). ^{1}H NMR (DMSO-d_6) δ 13.43 (br s, 1H), 12.21 (br s, 1H), 8.68 (m, 1H), 8.50 (s, 1H), 8.03 (m, 2H), 7.86 (d, 1H), 7.59 (d, 1H), 7.37 (t, 2H), 3.47 (q, 2H), 2.52 (m, 2H); ES-MS (m/z) 328 $[M+1]^+$.

EXAMPLE 89

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-(3-NITROPHENYL)CARBOXAMIDE



A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)1-N-(3-nitrophenyl)carboxamide

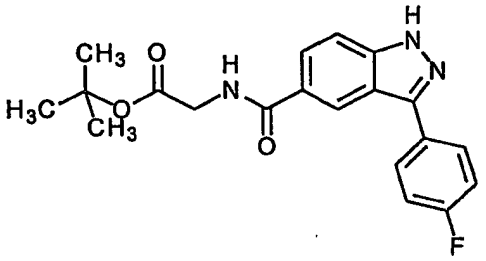
To a solution containing 3-nitroaniline (96 mg, 0.694 mmol) in pyridine (5 mL) was added 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (200 mg,

0.631 mmol). The reaction mixture was allowed to stir for 18 hours at ambient temperature. Water (30 mL) was then added and the resulting precipitate was filtered and dried to afford the title compound. This precipitate was taken on directly to the next step for deprotection.

To the previous precipitate was added 0.3% ammonia in methanol (10 mL). The solution was brought to 60°C for three hours. The resulting precipitate was filtered and dried to provide the title compound (140 mg, 60% overall yield). ^{1}H NMR (DMSO-d_6) δ 13.55 (br s, 1H), 10.76 (s, 1H), 8.78 (s, 1H), 8.70 (s, 1H), 8.20 (m, 1H), 8.11 (m, 2H), 8.00 (m, 2H), 7.68 (m, 2H), 7.40 (m, 2H); ES-MS (m/z) 377 $[M+1]^+$.

EXAMPLE 90

SYNTHESIS OF TERT-BUTYL-2-{[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO}ACETATE

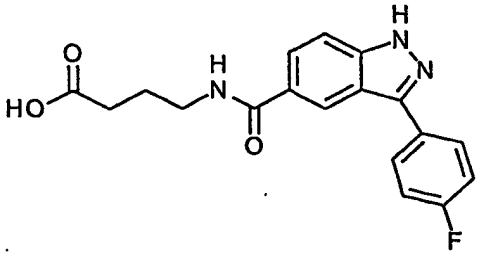


A. tert-Butyl 2-{[3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}acetate

The title compound was prepared as described in Example 86 A, using t-butyl glycine (112 mg, 0.858 mmol) (80 mg, 30%). ES-MS (m/z) 370$[M+1]^+$.

EXAMPLE 91

SYNTHESIS OF 4-{[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO} BUTANOIC ACID



A. Methyl 4-{[1-acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}butanoate

To a solution containing methyl 4-aminobuytrate hydrochloride (106.6 mg, 0.694 mmol) in pyridine (5 mL) was added 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (200 mg, 0.631 mmol). The reaction mixture was allowed to stir at ambient temperature for 18 hours. Water (40 mL) was added to the reaction mixture to afford a precipitate. The precipitate was filtered and dried to provide the title compound. The title compound was taken to the deprotection step. ES-MS (m/z) 398 $[M+1]^+$.

B. Methyl 4-{[3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}butanoate

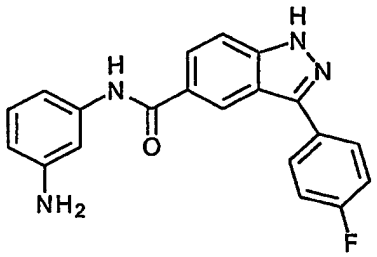
Example 91 A in 0.3% ammonia in methanol (10 mL) was allowed to stir at 60°C for three hours. Water (40 mL) was added and the resulting solution was extracted with ethyl acetate. The extracts were dried over sodium sulfate, filtered and removed to give a precipitate (50 mg). The title compound was taken to the next step. ES-MS (m/z) 356 $[M+1]^+$.

C. 4-{[3-(4-Fluorophenyl)-1H-indazol-5-yl]carbonylamino}butanoic acid

The title compound was prepared as described in Example 48 A (21 mg, 44%). ^{1}H NMR (DMSO-d_6) δ 13.42 (br s, 1H), 12.02 (br s, 1H), 8.61 (br s, 1H), 8.50 (s, 1H), 8.04 (t, 2H), 7.89 (d, 1H), 7.58 (d, 1H), 7.37 (t, 2H), 2.27 (t, 2H), 1.75 (m, 2H); ES-MS (m/z) 342 $[M+1]^+$.

EXAMPLE 92

SYNTHESIS OF N-(3-AMINOPHENYL)[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]CARBOXAMIDE



A. [1-Acetyl-3-(4-fluorophenyl)(1H-indazol-5-yl)1-N-(3-nitrophenyl)carboxamide

The title compound was prepared as described in Example 91 A and was taken on to the next step (quantitative yield). ES-MS (m/z) 419$[M+1]^+$.

B. N-(3-Nitrophenyl)[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide

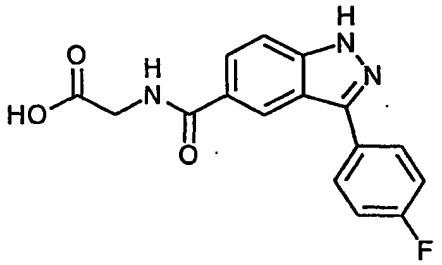
The title compound was prepared as described in Example 14 B (140 mg). ES-MS (m/z) 377 $[M+1]^+$.

C. N-(3-Aminophenyl)[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide

The title compound was prepared as described in Example 19 B (39.5 mg, 33%). ^{1}H NMR (DMSO-d_6) δ 13.47 (br s, 1H), 10.04 (s, 1H), 8.59 (s, 1H), 8.08 (t, 2H), 7.93 (d, 1H), 7.65 (d, 1H), 7.38 (t, 2H), 7.07 (s, 1H), 6.29 (d, 1H), 5.10 (br s, 2H); ES-MS (m/z) 347 $[M+1]^+$.

EXAMPLE 93

SYNTHESIS OF 2-{[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO}ACETIC ACID

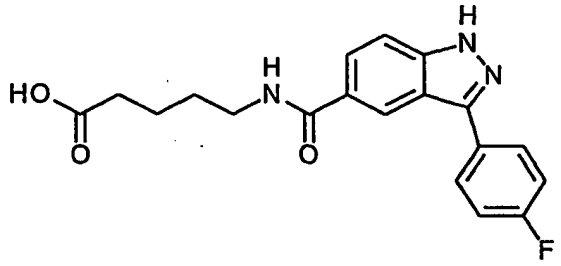


A. 2-{[3-(4-Fluorophenyl)-1H-indazol-5-yl]carbonylamino}acetic acid

Using Example 90 A (169 mg, 0.457 mmol), the title compound was prepared, except that an extraction with ethyl acetate was used to afford the title compound (77 mg, 54%). ^{1}H NMR (DMSO-d_6) δ 13.47 (br s, 1H), 12.58 (br s, 1H), 8.98 (s, 1H), 8.05 (s, 2H), 7.89 (m, 1H), 7.61 (m, 1H), 7.37 (br s, 2H), 3.93 (s, 2H); ES-MS (m/z) 314 $[M+1]^+$.

EXAMPLE 94

SYNTHESIS OF 5-{[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO}PENTANOIC ACID



A. Methyl 4-{[1-acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}butyrate

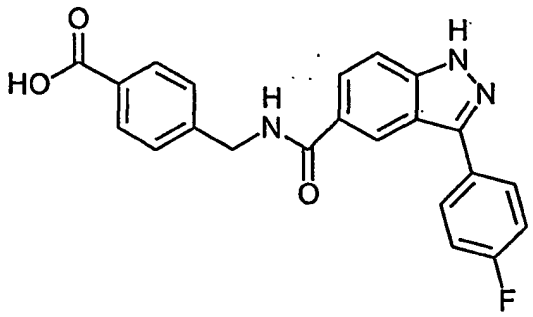
The title compound was prepared as described in Example 91 A, using methyl 5-amino valerate ester (91 mg, 0.694 mmol) to afford the title compound (105 mg, 40%).

B. 5- {[3-(4-Fluorophenyl)-1H-indazol-5-yl]carbonylamino}pentanoic acid

The title compound was prepared as described in Example 91 A to afford the title compound (77 mg, 100%). ^{1}H NMR (DMSO-d_6) δ 13.43 (s, 1H), 12.02 (br s, 1H), 8.58 (s, 1H), 8.50 (s, 1H), 8.02 (s, 2H), 7.87 (d, 1H), 7.58 (d, 1H), 7.37 (t, 2H), 3.57 (s, 1H), 2.23 (m, 2H), 1.53 (m, 4H); ES-MS (m/z) 356 $[M+1]^+$.

EXAMPLE 95

SYNTHESIS OF 4-({[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO}METHYL)BENZOIC ACID



A. Methyl 4-({1-acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}methyl)benzoate

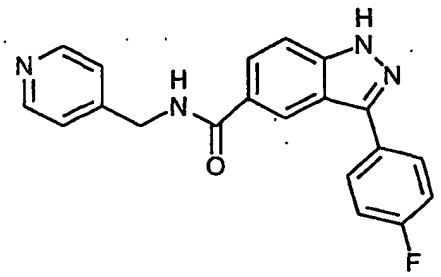
The title compound was prepared as described in Example 91 A, using methyl-4(aminomethyl)benzoate (129 mg, 0.642 mmol) and was taken on to the next step. ES-MS (m/z) 446 $[M+1]^+$.

B. Methyl 4-({[(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}methyl benzoate

The title compound was prepared as described in Example 14 B, using the title compound from Example 95 A (118 mg, 50% overall). ^{1}H NMR (DMSO-d_6) δ 13.47 (br s, 1H), 12.86 (br s, 1H), 9.24 (s, 1H), 8.60 (s, 1H), 7.96 (m, 5H), 7.62 (d, 1H), 7.41 (m, 3H), 4.56 (s, 2H); ES-MS (m/z) 390 $[M+1]^+$.

EXAMPLE 96

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-(4-PYRIDYLMETHYL)CARBOXAMIDE



A. [1-Acetyl-3-(4-fluorophenyl)(1H-indazol-5-yl)]-N-(4-pyridylmethyl)carboxamide

The title compound was prepared as described in Example 91 A, using (4-(aminomethyl)pyridine (75 mg, 0.694 mmol), except that the resulting solid was extracted with
5% sodium carbonate solution and ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to afford the title compound (130 mg, 53%). ES-MS (m/z) 389 $[M+1]^+$.

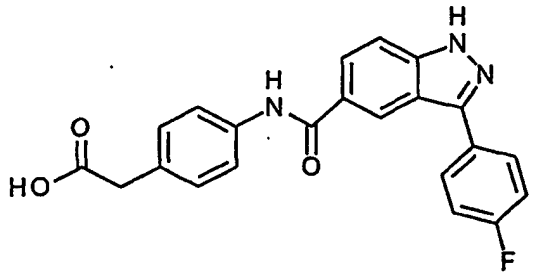
B. [3-(4-Fluorophenyl)(1H-indazol-5-yl)]-N-(4-pyridylmethyl)carboxamide

The title compound was prepared as described in Example 14 B, except that the resulting solution was extracted with ethyl acetate. The extracts were dried over sodium

sulfate, filtered and condensed to afford the title compound after trituration with hexanes (55 mg, 47%). ^{1}H NMR (DMSO-d_6) δ 13.47 (s, 1H), 9.25 (s, 1H), 8.61 (s, 1H), 8.47 (m, 2H), 7.92 (m, 3H), 7.62 (d, 1H), 7.32 (m, 4H), 4.52 (m, 2H); ES-MS (m/z) 347 $[M+1]^+$.

EXAMPLE 97

SYNTHESIS OF 2-(4-{[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]CARBONYLAMINO}PHENYL)ACETIC ACID



A. Ethyl 2-(4-{[1-acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}phenyl)acetate

The title compound (115 mg, 46%) was prepared as described in Example 91 A, using ethyl 4-aminophenyl acetate (112 mg, 0.673 mmol). ES-MS (m/z) 460 $[M+1]^+$.

B. Ethyl 2-(4-{[3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}phenyl)acetate

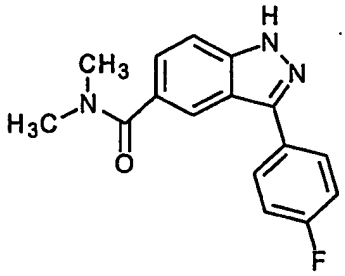
The title compound (25 mg, 27%) was prepared as described in Example 14 B, except that the precipitate was purified using preparative HPLC. It was then taken to the next step. ES-MS (m/z) 418 $[M+1]^+$.

C. 2-(4-{[3-(4-Fluorophenyl)-1-H-indazol-5-yl]carbonylamino}phenyl)acetic acid

The title compound was prepared as described in Example 48 A (6 mg, 26% overall). ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 12.30 (br s, 1H), 10.03 (s, 1H), 8.01 (m, 3H), 7.68 (m, 3H), 7.38 (t, 2H), 7.23 (m, 2H), 3.51 (s, 2H), ES-MS (m/z) 390 $[M+l]^+$.

EXAMPLE 98

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N,N-DIMETHYLCARBOXAMIDE

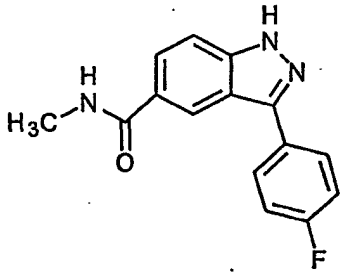


A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)1-N,N-dimethylcarboxamide

The title compound (163mg, 73%) was prepared as described in Example 91 A, using 2.0 M dimethylamine in THF (1.5 mL) to afford the title compound. ^{1}H NMR (DMSO-d_6) δ 13.40 (s, 1H), 8.00 (m, 3H), 7.59 (t, 1H), 7.43 (m, 1H), 7.31 (m, 2H), 3.29 (s, 6H); ES-MS (m/z) 284 $[M+1]^+$.

EXAMPLE 99

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-METHYLCARBOXAMIDE

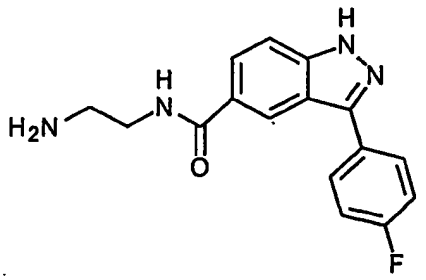


A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)]-N-methylcarboxamide

The title compound was prepared as described in Example 91 A, using 2.0M methylamine in tetrahydrofuran (1.26 mL), except the solution was extracted with 5% sodium carbonate and ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to afford a solid. The solid was purified by trituration using dichloromethane and hexanes to afford the title compound (33 mg, 19% yield). ^{1}H NMR (DMSO-d_6) δ 13.41 (s, 1H), 8.49 (m, 2H), 8.03 (m, 2H), 7.86 (m, 1H). 7.58 (m, 1H), 7.36 (t, 2H), 2.79 (s, 3H); ES-MS (m/z) 270$[M+1]^+$.

EXAMPLE 100

SYNTHESIS OF N-(3-AMINOETHYL)[3-(4-FLUOROPHENYL) (1H-INDAZOL-5-YL)]CARBOXAMIDE



A. N-{2-[(tert-Butoxy)carbonylamino]ethyl} [3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide

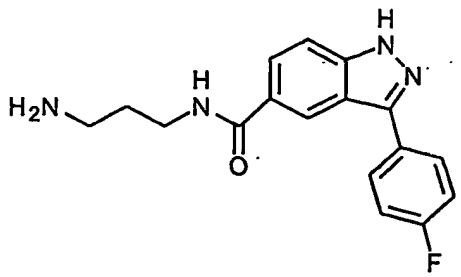
The title compound was prepared as described in Example 91 A, using N-(2-aminoethyl)carbamic acid tert-butyl ester (400 mg, 2.52 mmol), except that the reaction mixture was extracted with 5% sodium carbonate and ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to afford the title compound. The solid was taken on to the following step without purification. ES-MS (m/z) 399 $[M+1]^+$.

B. N-(3-Aminoethy)[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide

The solid from Example 100 A was dissolved in tetrahydrofuran (3mL) and trifluoroacetic acid (6 mL) and allowed to stir at ambient temperature for 18 hours. The reaction mixture was neutralized and extracted with 5% sodium carbonate and ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to afford the title compound (150 mg, 80% overall). ES-MS (m/z) 299 $[M+1]^+$.

EXAMPLE 101

SYNTHESIS OF N-(3-AMINOPROPYL)[3-(4-FLUOROPHENYL) (1H-INDAZOL-5-YL)]CARBOXAMIDE



A. N-{3-[(tert-Butoxy)carbonylamino]propyl}[3-(4-fluorophenyl)(1H-indazol-5-yl)carboxamide

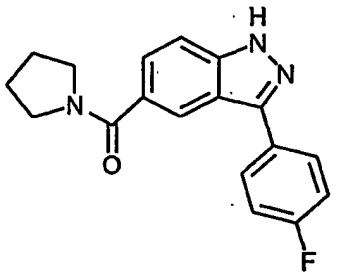
The title compound was prepared as described in Example 100 A, using N-(2-aminopropyl)carbamic acid tert-butyl ester (430 mg, 2.52 mmol) and was taken on to the next step. ES-MS (m/z) 413 $[M+1]^+$.

B. N-(3-Aminopropyl)[3-(4-fluorophenyl)(1H-indazole-5-yl)]carboxamide

The title compound was prepared as described in Example 100 B (193 mg, 97% overall). ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 8.78 (m, 1H), 8.52 (s, 1H), 7.90 (m, 6H), 7.36 (m, 2H), 2.83 (m, 2H), 1.80 (m, 2H), 1.96 (s, 1H), 1.13 (m, 1H); ES-MS (m/z) 313 $[M+1]^+$.

EXAMPLE 102

SYNTHESIS OF 3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL) PYRROLIDINYL KETONE

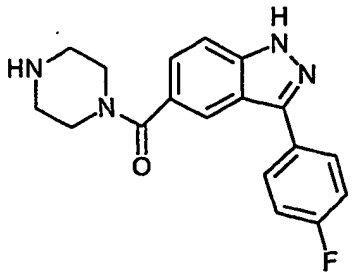


A. 3-(4-Fluorophenyl)(1H-indazol-5-yl) pyrrolidinyl ketone

The title compound was prepared as described in Example 91 A, using pyrrolidine (49.3 mg, 0.694 mmol). After 18 hours of reaction time, ammonium hydroxide (3 drops) was added to the solution. Stirring continued for an additional 2 hours. The reaction mixture was extracted with 5% sodium carbonate and ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to give an oil. The oil was purified by trituration with dichloromethane and hexanes to provide the title compound (129 mg, 66% yield). ^{1}H NMR (DMSO-d_6) δ 13.39 (s, 1H), 8.14 (s, 1H), 8.00 (m, 2H), 7.55 (q, 2H), 7.32 (t, 2H), 3.44 (m, 4H), 1.79 (m, 4H); ES-MS (m/z) 310 $[M+1]^+$.

EXAMPLE 103

SYNTHESIS OF 3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)PIPERAZINYL KETONE



A. tert-Butyl 4-{[1-acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonyl}piperazinecarboxylate

The title compound (130 mg, 32%) was prepared as described in Example 100 A, using tert-butyl 1-piperazine carboxylate (129 mg, 0.694 mmol) and trituration with dichloromethane and hexanes. ES-MS (m/z) 482 $[M+1]^+$.

B. 1 -Acetyl-3-(4-fluorophenyl)-5-(piperazinylcarbonyl)-1H-indazole

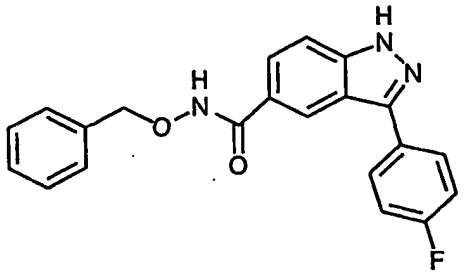
The title compound was prepared as described in Example 100 B, except that the solid was purified by trituration with dichloromethane and hexanes (120 mg). ES-MS (m/z) 367$[M+1]^+$.

C. 3-(4-Fluorophenyl)(1H-indazol-5-yl)piperazinyl ketone

The title compound was prepared as described in Example 14 B, using 0.3% ammonium hydroxide in methanol (6 mL). The methanol was then removed and the resulting solid was purified by trituration with dichloromethane and hexanes to afford the title compound (24 mg, 23%). ^{1}H NMR (DMSO-d_6) δ 13.53 (s, 1H), 8.11 (s, 1H), 8.00 (m, 2H), 7.62 (d, 1H), 7.44 (m, 1H), 7.34 (m, 2H), 3.72 (br, 4H), 3.10 (m, 4H); ES-MS (m/z) 325 $[M+1]^+$.

EXAMPLE 104

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-(PHENYLMETHOXY)CARBOXAMIDE

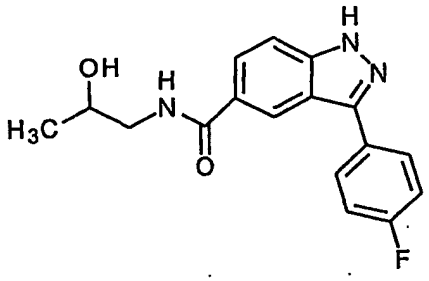


A. [3-(4-Fluorophenyl)(1H-indazol-5-yl)]-N-(phenylmethoxy)carboxamide.

The title compound (166 mg, 73%) was prepared as described in Example 102 A, except that an additional drop of ammonium hydroxide was added. ES-MS (m/z) 362 $[M+1]^+$.

EXAMPLE 105

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-(2-HYDROXYPROPYL)CARBOXAMIDE

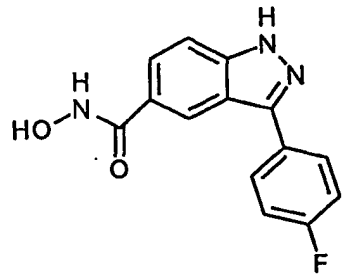


A. [3-(4-fluorophenyl)(1H-indazol-5-yl)]-N-(2-hydroxypropyl)carboxamide

The title compound (68 mg, 28% yield) was prepared as described in Example 86 A, using 1-amino-2-propanol (64 mg, 0.852 mmol) and triethyl amine (3 drops) in lieu of 4-(dimethylamino)pyridine. ES-MS (m/z) 314$[M+1]^+$.

EXAMPLE 106

SYNTHESIS OF 3-(4-FLUOROPHENYL)-1H-INDAZOLE-5-CARBOHYDROXAMIC ACID

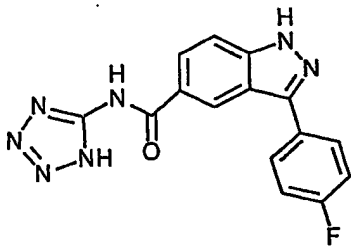


A. 3-(4-fluorophenyl)-1H-indazole-5-carbohydroxamic acid

To a solution containing [3-(4-fluorophenyl)(1H-indazol-5-yl)]-N-phenylmethoxy)carboxamide (140 mg, 0.388 mmol) in ethyl acetate (10 mL) was added palladium on activated carbon (10%, 30mg). The reaction mixture was stirred at ambient temperature for 18 hours. It was filtered with celite and washed with ethyl acetate. The filtrate was concentrated to give the title compound (35 mg, 33%). ES-MS (m/z) 272 $[M+1]^+$.

EXAMPLE 107

SYNTHESIS OF N-(2H-1,2,3,4-TETRAZOL-5-YL) [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]CARBOXAMIDE

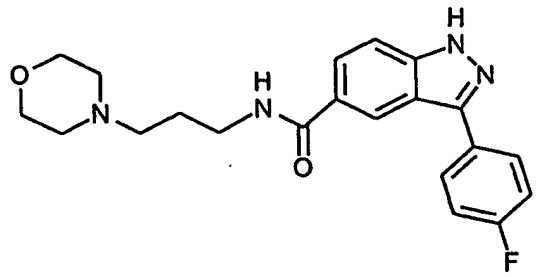


A. N-(2H-1,2,3,4-Tetrazol-5-yl)[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide

The title compound was prepared as described in Example 86 A, except that 4-(dimethylamino)pyridine was omitted, and purified by preparative HPLC (20 mg, 6% yield). ^{1}H NMR (DMSO-d_6) δ 13.61 (br s, 1H), 12.52 (br s, 1H), 8.89 (s, 1H), 8.06 (m, 3H), 7.71 (d, 1H), 7.40 (t, 2H); ES-MS (m/z) 324 $[M+1]^+$.

EXAMPLE 108

SYNTHESIS OF {3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)}-N-(3-MORPHOLIN-4-YLPROPYL)CARBOXAMIDE



A. 1-Acetyl-3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid

To a flask containing 3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid (5.0 g, 0.02 mol) was added acetic acid (100 mL). The flask was placed under nitrogen and to the flask was added acetic anhydride (5.6 mL, 0.06 mol). The reaction refluxed at 80° C for three hours. The flask was cooled to room temperature and the reaction was diluted with water. The product was collected by vacuum filtration and rinsed with additional amounts of water to yield the title compound (5.96g, 100% yield) ^{1}H NMR (DMSO-d_6) δ 8.6 (s, 1H), 8.45-8.5 (d, 1H), 8.2-8.25 (d, 1H), 8.1 (m, 2H), 7.5 (t, 2H), 2.8 (s, 3H).

B. 1 -Acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride

To a flask containing 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carboxylic acid (1.5g, 5.9 mmol) was added dichloromethane (80 mL) and oxalyl chloride (1.02 mL, 11.7 mmol). The reaction was allowed to stir under a nitrogen atmosphere overnight. To the flask was added a catalytic amount of DMF. The reaction was allowed to stir for three hours. TLC indicated reaction was complete. The solvent was removed and a solid formed to yield the title compound (1.57g, 84% yield).

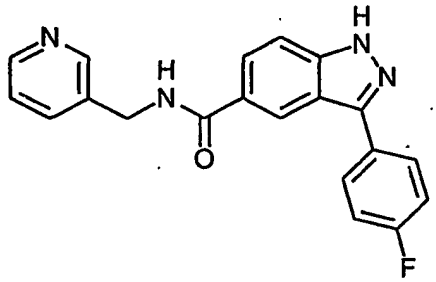
C. {3-(4-Fluorophenyl)(1H-indazol-5-yl)}-N-(3-morpholin-4-ylpropyl)carboxamide

To a flask containing a solution of 4-(3-Aminopropyl)-morpholine (117 µl, 0.79 mmol) in pyridine (1 mL) was added 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (230 mg, 0.72 mmol) dissolved in pyridine (5 mL). The reaction was allowed to stir under a nitrogen atmosphere overnight. The reaction was not complete so an additional equivalent of 4-(3-Aminopropyl)-morpholine (100 µl, 0.72 mmol) was added. The reaction was allowed to stir at room temperature overnight. LCMS showed the product

formation. Solvent was removed by rotary evaporation. The reaction was treated with water and the product was extracted with ethyl acetate and dichloromethane. The organic layers were combined and washed with saturated aqueous sodium carbonate solution and brine. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield the product. This was purified by semi-preparative HPLC. The product was washed with a sodium bicarbonate solution to remove the TFA salt to yield the title compound (37.3 mg, 13.5% yield). ^{1}H NMR (DMSO-d_6) δ 8.6 (m, 1H), 8.5 (m, 1H), 8.0 (m, 2H), 7.9 (m, 1H), 7.7 (m, 1H), 7.4 (m, 2H), 3.3 (m, 4H), 3.1 (m, 2H), 2.3 (m, 6H), 1.6 (m, 2H) ES-MS m/z 383 $[M+1]^+$.

EXAMPLE 109

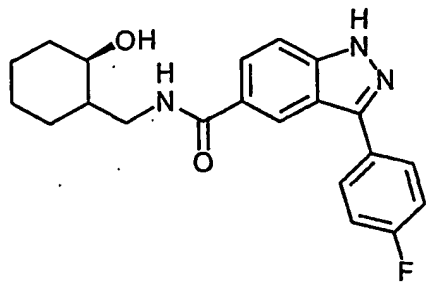
SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)}-N-(3-PYRIDYLMETHYL)CARBOXAMIDE



To a flask containing 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (300 mg, 0.95mmol) dissolved in pyridine (4 mL) was added 3-aminomethyl pyridine (106 µl, 1.05 mmol). The reaction was allowed to stir under a nitrogen atmosphere overnight. LCMS indicated the reaction was complete. Solvent was removed and water was added to the flask. A solid crashed out of solution that was collected by filtration. The solid was taken up in a 3% ammonia in methanol solution (8mL) and allowed to reflux at 60°C for three hours. The reaction was neutralized with 1 N HCl solution and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield the title compound (134 mg, 41% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 9.2 (s, 1H), 8.6 (m, 2H), 8.5 (s, 1H), 8.1 (m, 2H), 7.95 (d, 1H), 7.65 (d, 1H), 7.6 (m, 1H), 7.4 (m, 3H), 4.6 (m, 2H) ES-MS m/z 347 $[M+1]^+$.

EXAMPLE 110

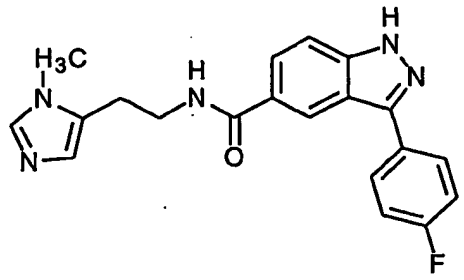
SYNTHESIS OF N-[((2R)-2-HYDROXYCYCLOHEXYL)METHYL] [3-(4-FLUOROPHENYL) (1H-INDAZOL-5-YL)]CARBOXAMIDE



To a flask containing 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (330 mg, 0.95mmol) dissolved in pyridine (6 mL) was added trans-2-aminomethyl-1-cyclohexanol (135.6 mg, 1.05 mmol). The reaction was allowed to stir under a nitrogen atmosphere overnight. Solvent was removed and the reaction was extracted with ethyl acetate. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, dried with magnesium sulfate, filtered and concentrated to yield the crude product. The product was purified by column chromatography (SiO_2, 5% methanol in dichloromethane). The compound was taken up in a 3% ammonia in methanol solution (8mL) and allowed to reflux at 60°C for three hours. The reaction was neutralized with 1 N HCl solution and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield the title compound (240 mg, 69% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.6 (s, 2H), 8.1 (m, 2H), 7.9 (d, 1H), 7.6 (d, 1H), 7.4 (m, 2H), 4.8 (s, 1H), 3.5 (m, 1H), 3.2 (m, 1H), 1.8 (m, 2H), 1.6 (m, 2H), 1.4 (m, 2H), 0.8-1.0 (m, 3H), ES-MS m/z 368 $[M+1]^+$.

EXAMPLE 111

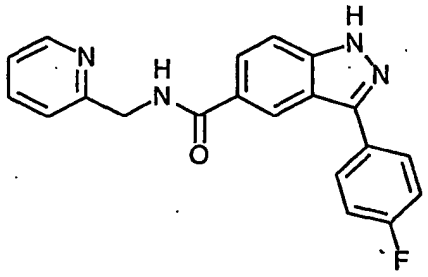
SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-[2-(1-METHYLIMIDAZOL-5-YL)ETHYL]CARBOXAMIDE)



The product was synthesized as described in Example 109 using 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (142.5 mg, 0.45 mmol) and 3-methylhistamine 100mg, 0.5 mmol). The product was purified by semipreparative HPLC (20-80% acetonitrile gradient over 30 minutes at 20mL/min) to yield the title compound (52 mg, 32 % yield). ^{1}H NMR (DMSO-d_6) δ 8.85 (s, lH), 8.5 (s, lH), 8.05 (m, 2H), 7.9 (d, lH), 7.7 (d, 1H), 7.4 (m, 3H), 3.9 (s, 3H), 3.6 (m, 2H), 3.0 (m, 2H). ES-MS m/z 364 $[M+1]^+$.

EXAMPLE 112

SYNTHESIS OF [3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-N-(2-PYRIDYLMETHYL)CARBOXAMIDE

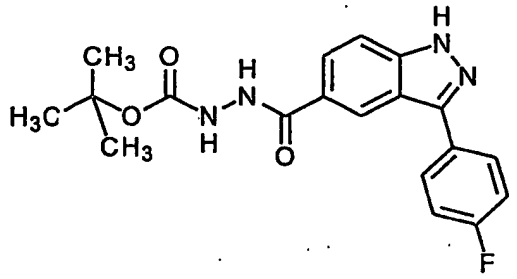


To a flask containing 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (300 mg, 0.95mmol) dissolved in pyridine (4 mL) was added 2-aminomethyl pyridine (106 µl, 1.02 mmol). The reaction was allowed to stir under a nitrogen atmosphere overnight. LCMS indicated the reaction was complete. Solvent was removed and water was added to the flask. A solid crashed out of solution that was collected by filtration. The

product was purified by column chromatography (SiO_2, 5% methanol in dichloromethane). The solid was taken up in 3 % ammonia in methanol solution (8 mL) and allowed to reflux at 60°C for three hours. The reaction was neutralized with 1 N HCl solution and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield the title compound (106 mg, 32 % yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 9.3 (t, 1H), 8.65 (s, lH), 8.5 (d, 1H), 8.1 (m, 2H), 8.0 (d, 1H), 7.75 (t, lH), 7.65 (d, 1H), 7.4 (m, 3H), 7.25 (t, 1H), 4.6 (d, 2H), ES-MS m/z 368 $[M+1]^+$.

EXAMPLE 113

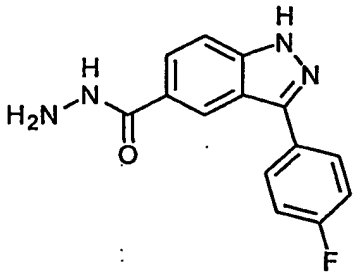
SYNTHESIS OF N-[(TERT-BUTOXY)CARBONYLAMINO] [3-(4-FLUOROPHENYL) (1H-INDAZOL-5-YL)]CARBOXAMIDE



The product was synthesized as described in Example 109 A using 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (500 mg, 1.58 mmol) and tert-butyl carbazate (230 mg, 1.74 mmol). ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1H), 8.95 (s, 1H), 8.4 (s, 1H), 8.1 (m, 2H), 7.9 (d, 1H), 7.65 (d, 1H), 7.4 (t, 2H), 1.3-1.5 (m, 9H), ES-MS m/z 371 $[M+1]^+$.

EXAMPLE 114

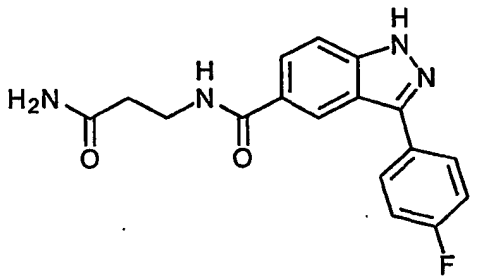
SYNTHESIS OF N-AMINO[3-(4-FLUOROPHENYL)(1 H-INDAZOL-5-YL)]CARBOXAMIDE



To a flask containing N-[(tert-butoxy)carbonylamino] [3-(4-fluorophenyl)(lH-indazol-5-yl)]carboxamide (230 mg, 0.62 mmol) was added 4 N HC1 in dioxane (6 mL). The reaction was allowed to stir for four hours. The reaction was treated with 10% sodium hydroxide solution to make the reaction slightly basic. The solvent was removed and the reaction was diluted with water and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered and concentrated to yield the title compound (153 mg, 91.6 % yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 9.9 (s, 1H), 8.55 (s, 1H), 8.1 (m, 2H), 7.9 (d, lH), 7.65 (d, 1H), 7.4 (t, 2H), 4.5 (bs, 1H), 3.6 (s, 1H), ES-MS m/z 271 $[M+H]^+$.

EXAMPLE 115

N-(2-CARBAMOYLETHYL)[3 -(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]CARBOXAMIDE



A. Tert-butyl 3- {[1-acetyl-3-(4-fluorophenyl)- 1H-indazol-5-yl]carbonylamino} propanoate

The title compound was prepared as described in Example 91 A, using H-β-Ala-O-tert-butyl hydrochloride (249 mg, 1.90 mmol) and 1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-carbonyl chloride (300 mg, 0.947 mmol). The reaction mixture was extracted with 5% sodium carbonate and ethyl acetate to afford the title compound (115 mg, 28%). ES-MS (m/z) 426$[M+1]^+$.

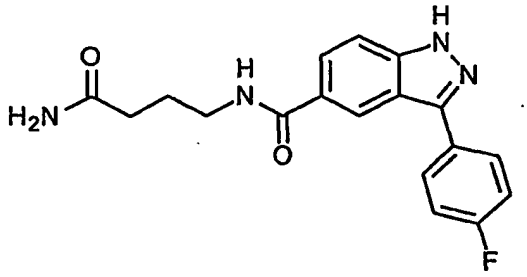
B. N-(2-carbamoylethyl)[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxainide

A sealed tube containing tert-butyl 3-{[1 -acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}propanoate (115 mg, 0.270 mmol) and methanol saturated with ammonium hydroxide (2 mL) was heated to 80°C for 18 hours. The solution was condensed to give an oil. The oil was dissolved in dimethyl formamide (5 mL) with N-N'-carbonyldiimidazole (110 mg). The solution was allowed to stir for two hours at ambient

temperature. Ammonium acetate (160 mg) was added and the reaction mixture was allowed to stir at ambient conditions under nitrogen for 18 hours. The mixture was condensed and extracted with 5% sodium bicarbonate and ethyl acetate. The extracts were dried over sodium sulfate, filtered and condensed to give the title compound (17 mg, 19% yield) after purification by preparative-HPLC. ^{1}H NMR (DMSO-d_6) δ 8.65 (br s, 1H), 8.47 (s, 1H), 8.00 (m, 2H), 7.84 (d, 1H), 7.59 (d, 1H), 7.43 (br, 1H), 7.35 (t, 2H), 6.84 (s, 1H), 3.45 (m, 2H), 2.39 (m, 2H); ES-MS (m/z) 327[M+1]$^+$.

EXAMPLE 116

N-(3-CARBAMOYLPROPYL)[3-(4-FLUOROPHENYL)(1 H-INDAZOL-5-YL)]CARBOXAMIDE



A. Methyl 4-{[1-acetyl-3-(4-fluorophenyl)-1H-indazol-5-yl]carbonylamino}butanoate

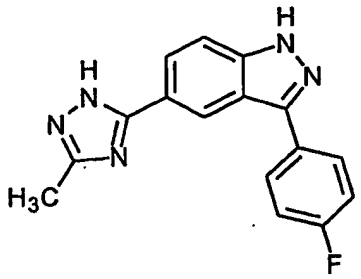
The title compound was prepared as described in Example 91 A, using methyl 4-amino butyrate hydrochloride (291 mg, 1.90 mmol), except that the solution was extracted with 5% sodium bicarbonate solution and ethyl acetate. The resulting solid was triturated with dichloromethane and hexanes to afford the title compound (95 mg, 25%). ES-MS (m/z) 398[M+1]$^+$.

B. N-(3-carbamoylpropyl)[3-(4-fluorophenyl)(1H-indazole-5-yl)]carboxamide

A sealed glass bomb containing methyl 4-{[1-acetyl-3-(4-fluorophenyl)-1H-indazole-5-yl]carbonylamino}butanoate (95 mg, 0.239 mmol) in methanol with saturated ammonia (7 mL) was heated to 80°C for 18 hours. The reaction mixture was condensed and the resulting solid was purified by HPLC to afford the title compound (35 mg, 43% yield). ^{1}H NMR (DMSO-d_6) δ 13.43 (br s, 1H), 8.50 (s, 1H), 8.04 (m, 2H), 7.87 (d, 1H), 7.58 (d, 1H), 7.37 (t, 1H), 7.29 (s, 1H), 6.75 (br s, 1H), 3.75 (m, 2H), 2.09 (t, 2H), 1.73 (t, 2H); ES-MS (m/z) 341[M+1]$^+$.

EXAMPLE 117

SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOLE-5-YL)]-3-METHYL-4H-1,2,4-TRIAZOLE



A. [3-(4-Fluorophenyl)inden-5-yl]-N-{(iminoethyl)amino]carboxamide

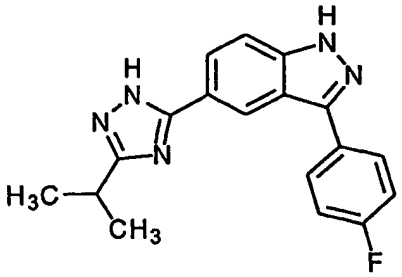
To a flask containing N-amino[3-(4-fluorophenyl)(1H-indazol-5-yl)]carboxamide (196 mg, 0.73 mmol) under a nitrogen atmosphere was added anhydrous ethanol (3mL) and triethylamine (0.1 mL, 0.73 mmol). In a separate flask ethyl acetimidate hydrochloride (90 mg, 0.73 mmol) was dissolved in anhydrous ethanol (2 mL) and triethylamine (0.1 mL, 0.73 mmol). The flask containing the N-amino[3-(4-fluorophenyl)(1H-indazole-5-yl)]carboxamide solution was placed on ice while the ethyl acetimidate hydrochloride solution was added dropwise to the chilled flask. The flask was kept at 0°C for 2 hours and then allowed to stir at room temperature for two days. LC-MS indicated the reaction was complete. The solvent was removed and the compound was taken on crude into the next step of the synthesis. ES-MS m/z 312 $[M+H]^+$.

B. 5-[3-(4-Fluorophenyl)(1H-indazole-5-yl)]-3-methyl-4H-1,2,4-triazole

In a flask containing [3-(4-fluorophenyl)inden-5-yl] -N-{(iminoethyl)amino]carboxamide (81 mg, 0.26 mmol) under a nitrogen atmosphere was added anhydrous dimethylformamide (5 mL). This was heated overnight at 110°C. In an additional flask [3-(4-fluorophenyl)inden-5-yl]-N- {(iminoethyl)amino]carboxamide (105 mg, 0.33mmol) was heated overnight in anhydrous dimethylformamide (5 mL) at 80°C. The solvents for both reaction were removed and the products combined. The combined product was purified by HPLC (20-100 acetonitrile gradient over 30 minutes at 20 mL/min) to yield the title compound (19 mg, 11% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.6 (s, 1H), 8.0-8.08 (m, 3H), 7.7 (d, 1H), 7.42 (t, 2H), 2.5 (s, 3H), ES-MS m/z 294 $[M+H]^+$.

EXAMPLE 118

SYNTHESIS OF 5-{3-(4-FLUOROPHENYL)(1H-INDAZOLE-5-YL)]-3-(METHYLETHYL)-4H-1,2,4-TRIAZOLE



A. Ethoxy[3-(4-fluorophenyl)(1H-indazole-5-yl)]methanimine hydrochloride

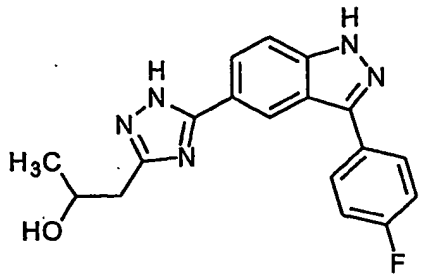
To a flask containing 3-(4-fluorophenyl-1H-indazole-5-carbonitrile (200 mg, 0.84 mmol) was added absolute ethanol (15 mL). The flask was placed in an ice bath and into the flask was bubbled hydrochloric acid gas until the solution became saturated. The reaction was allowed to stir under a nitrogen atmosphere overnight. LC-MS showed the reaction was complete. The solvent was removed and left on the pump to dry. The product was taken on crude into the next step of the synthesis ES-MS (m/z) 284.

B. 5-[3-(4-Fluorophenyl)(1H-indazole-5-yl}-3-(methylethyl)-4H-1,2,4-triazole

To a flask containing ethoxy[3-(4-fluorophenyl)(1H-indazole-5-yl)]methanimine hydrochloride (106 mg, 0.37 mmol) was added absolute ethanol (2.5 mL) and triethylamine (0.15 mL, 1.11mmol). The flask was placed on ice and to the flask was added a solution of isobutyric acid hydrazide (37.7 mg, 0.37mmol) in absolute ethanol was heated at 60°C for fifteen hours. An additional two equivalents of the isobutyric acid hydrazide (75 mg, 0.74 mmol) and triethylamine (0.2 mL, 1.35 mmol) was added to the reaction and allowed to stir overnight. Reaction was continuing to progress slowly, two equivalents of the isobutyric acid hydrazide (75 mg, 0.74 mmol) and triethylamine (0.2ml, 1.35 mmol) were added to the reaction and allowed to stir overnight. The reaction was stopped. Solvent was removed by rotary evaporation and the product was purified by HPLC to yield the title compound (53 mg, 45% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, lH), 8.6 (s,1H), 8.0-8.1 (m, 3H), 7.7 (m, 1H), 7.35-7.5 (m, 2H), 1.4 (m, 7H), ES-MS (m/z) 322 $[M+1]^+$.

EXAMPLE 119

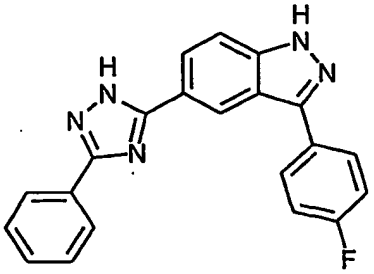
SYNTHESIS OF 1-{5-[3-(4-FLUOROPHENYL)-1H-INDAZOLE-5-YL]-4H-1,2,4-TRIAZOL-3-YL} PROPAN-2-OL



To a sealed tube containing ethoxy[3-(4-fluorophenyl)(1H-indazole-5-yl)]methanimine hydrochloride (300 mg, 0.94 mmol) dissolved in ethanol (15 mL) and triethylamine (0.3 µl, 2.82 mmol) was added a solution of 3-hydroxybutyric acid hydrazide (190 mg, 1.5 mmol) in ethanol. The reaction was sealed and allowed to stir at 70°C overnight. Solvent was removed and the product was purified via HPLC to yield the title compound. ^{1}H NMR (DMSO-d_6) δ 8.7 (s, 1H), 8.1 (m, 3H), 7.75 (d, 1H), 7.4 (t, 2H), ES-MS (m/z) 338 $[M+1]^+$.

EXAMPLE 120

SYNTHESIS OF 5-{3-(4-FLUOROPHENYL)(1H-INDAZOLE-5-YL)]-3-PHENYL-4H-1,2,4-TRIAZOLE

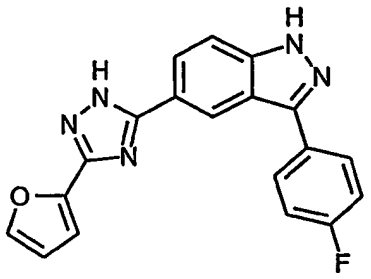


The procedure described in example 119 using ethoxy[3-(4-fluorophenyl)(1H-indazole-5-yl)]methanimine hydrochloride (200 mg, 0.62 mmol), triethylainine (0.25 mL, 1.86 mmol) and benzoic hydrazide (170 mg, 1.25 mmol) was

followed to yield the title compound (105 mg, 48% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 8.74 (s, 1H), 8.0-8.2 (m, 5H), 7.75 (d, 1H), 7.35-7.6 (m, 5H), ES-MS (m/z) 356 $[M+1]^+$.

EXAMPLE 121

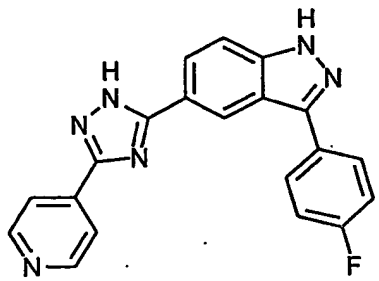
SYNTHESIS OF 2-{5-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-4H-1,2,4-TRIAZOL-3-YL} FURAN



The procedure described in example 119 using ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methanimine hydrochloride (200 mg, 0.62 mmol), triethylainine (0.25 mL, 1.86 mmol) and 2-furoic acid hydrazide (157.6 mg, 1.25 mmol) was followed to yield the title compound (32 mg, 15% yield). ^{1}H NMR (DMSO-d_6) δ 14.8 (br s, 1H), 13.5 (s, 1H), 8.7 (s, 1H), 8.0-8.15 (m, 3H), 7.78 (s, 1H), 7.75 (d, 1H), 7.4 (t, 2H), 7.0 (br s, 7.0), 6.65 (s, 1H), ES-MS (m/z) 346 $[M+1]^+$.

EXAMPLE 122

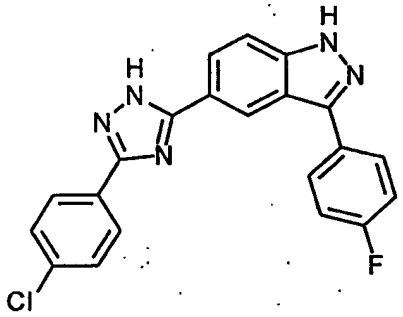
SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-3-(4-PYRIDYL)-4H- 1,2,4-TRIAZOLE



The procedure described in example 119 using ethoxy[3-(4-fluorophenyl)(1H-indazole-5-yl)]methanimine hydrochloride (200 mg, 0.62 mmol), triethylainine (0.25 mL, 1.86 mmol) and isonicotinic acid hydrazide (171.42 mg, 1.25 mmol) was followed to yield the title compound (34 mg, 15% yield). ^{1}H NMR (DMSO-d_6) δ 13.6 (s, 1H), 8.78-8.82 (m, 3H), 8.05-8.25 (m, SH), 7.8 (d, 1H), 7.45 (t, 2H), ES-MS (m/z) 357 $[M+1]^+$.

EXAMPLE 123

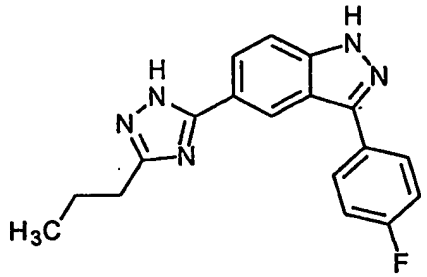
SYNTHESIS OF 3-(4-CHLOROPHENYL)-5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-4H-1,2,4-TRIAZOLE



To a sealed tube containing ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methanimine hydrochloride (300 mg, 0.94 mmol) dissolved in ethanol (15 mL) and triethylamine (0.3 µL, 2.82 mmol) was added 4-chlorobenzoic hydrazide (213 mg, 1.25 mmol). The tube was sealed and allowed to stir at 75°C overnight. The solvent was removed and the material was purified by HPLC to yield the title compound (46 mg, 19% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.75 (s, 1H), 8.0-8.2 (m, 5H), 7.76 (d, 1H), 7.6 (m, 2H), 7.4-7.42 (t, 2H), ES-MS (m/z) 390 $[M+1]^+$.

EXAMPLE 124

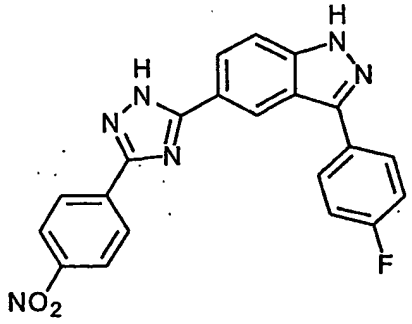
SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-3-PROPYL-4H-1,2,4-TRIAZOLE



The procedure described in example 123 using ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methanimine hydrochloride (200 mg, 0.62 mmol), triethylamine (0.25 mL, 1.86 mmol) and butyric acid hydrazide (127. 7 mg, 1.25 mmol) was used to prepare the title compound (16 mg, 8% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s,1H), 8.6 (s, 1H), 8.0-8.1 (m, 3H), 7.68-7.7 (d, 1H), 7.42 (t, 2H), 2.7 (t, 2H), 1.75 (m, 2H), 0.95 (t, 3H), ES-MS (m/z) 322 $[M+l]^+$.

EXAMPLE 125

SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOLE-5-YL)]-3-(4-NITROPHENYL)-4H- 1,2,4-TRIAZOLE

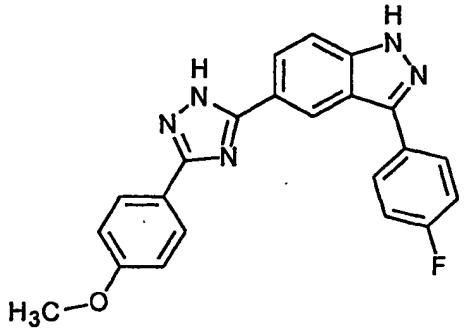


The procedure described in example 123 using ethoxy[3-(4-fluorophenyl)(1H-indazole-5-ylyimethanimine hydrochloride (400 mg, 1.25 mmol), triethylamine (0.5 mL, 3.7 mmol) and 4-nitrobenzoic hydrazide(452 mg, 2.5 mmol) was used to prepare the title compound (167 mg, 33% yield). ^{1}H NMR (DMSO-d_6) δ 14.9 (bs, 1H),

13.6 (s, 1H), 8.79 (s, 1H), 8.4 (s, 4H), 8.05-8.2 (m, 3H), 7.8 (d, 1H), 7.45 (t, 2H), ES-MS (m/z) 401 $[M+1]^+$.

EXAMPLE 126

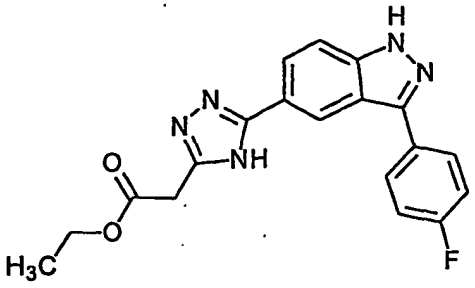
SYNTHESIS OF 1- {5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)](4H-1,2,4-TRIAZOL-3-YL)]-4-METHOXYBENZENE



The procedure described in example 123 using ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methanimine hydrochloride (400 mg, 1.25 mmol), triethylamine (0.5 mL, 3.7 mmol) and 4-methoxy benzhydrazide (415mg, 2.5 mmol) was used to prepare the title compound (175 mg, 37% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.71 (s, 1H), 8.16 (d, 1H), 8.0-8.1 (m, 4H), 7.75 (d, 1H), 7.45 (t, 2H), 7.1 (d, 2H), 3.88 (s, 3H), ES-MS (m/z) 386 $[M+1]^+$.

EXAMPLE 127

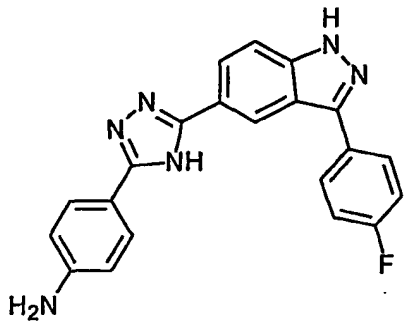
SYNTHESIS OF ETHYL-2-{5-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-4H-1,2,4-TRIAZOL-3-YL}ACETATE



The procedure described in Example 123 using ethoxy[3-(4-fluorophenyl)(1H-indazole5-yl)]methanimine hydrochloride (400 mg, 1.25 mmol), triethylamine (0.5 mL, 3.7 mmol) and 4-methoxy benzhydrazide (415mg, 2.5 mmol) was used to prepare the title compound (195 mg, 43% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.62 (s, 1H), 8.05 (t, 3H), 7.65 (d, 1H), 7.41 (t, 2H), 4.15 (q, 2H), 3.9 (s, 2H), 1.2 (t, 3H), ES-MS (m/z) 366 $[M+1]^+$.

EXAMPLE 128

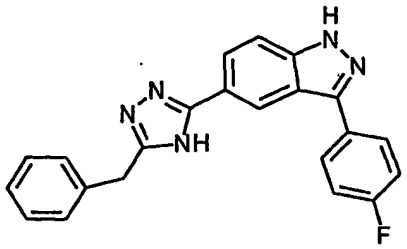
SYNTHESIS OF 4-{5-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-4H-1,2,4-TRIAZOL-3-YL}PHENYLAMINE



To a flask containing 5-[3-(4-fluorophenyl)(1H-indazol-5-yl)]-3-(4-nitrophenyl)-4H-1,2,4-triazole (60 mg) was added ethyl acetate (15 ml). The flask was evacuated and purged with nitrogen. To the flask was added palladium on carbon catalyst (10mg). The reaction was placed under a hydrogen atmosphere and allowed to stir overnight. The reaction was filtered through celite and the organic layer was concentrated. The product was purified by HPLC to yield the title compound (15 mg, 26% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.65 (s, 1H), 8.1 (d, 1H), 8.05 (t, 2H), 7.77 (d, 2H), 7.7 (d, 1H), 7.4 (t, 2H), 6.7 (d, 2H), ES-MS (m/z) 371 $[M+1]^+$.

EXAMPLE 129

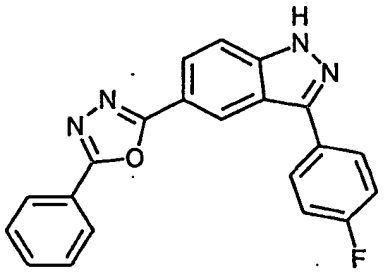
SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-3-BENZYL-4H-1,2,4-TRIAZOLE



The procedure described in example 123 using ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methanimine hydrochloride (200 mg, 0.62 mmol), triethylamine (0.25 mL, 1.86 mmol) and phenyl acetic hydrazide (187mg, 1.25 mmol) was used to prepare the title compound (101 mg, 44% yield). ^{1}H NMR (DMSO-d_6) δ 8.7 (s, 1H), 8.05 (m, 3H), 7.5 (d, 1H), 7.2-7.5 (m, 7H), 4.15 (s, 2H), ES-MS(m/z) 370 $[M+1]^+$.

EXAMPLE 130

SYNTHESIS OF 2-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-5-PHENYL-1,3,4-OXADIAZOLE



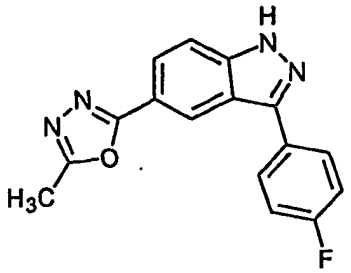
A. 2-[3-(4-Fluorophenyl)(1H-indazol-5-yl)]-5-phenyl-1,3,4-oxadiazole

To a solution of phenyl hydrazide (68 mg, 0.5 mmol) in pyridine (3 mL) was added N-acetyl,3-F-Phenyl-5-carbonyl chloride indazole (150 mg, 0.5 mmol). The solution was stirred overnight at room temperature when water (30 mL) was added and the solid was filtered and dried in a vacuum oven (40°C). The solid was then taken up in thionyl chloride (20 mL) and refluxed for 3 hours when the solvent was removed. The crude reaction mixture was then chromatographed on silica gel eluting with 15% methanol in methylene chloride to recover the acetylated product. The solid was taken up in methanol (30 mL) and saturated

ammonium hydroxide (3 mL) and stirred at room temperature for 3 hours when it was diluted with water (100 mL) and filtered. The title product was then dried in a vacuum oven to give 90 mg of said material (50% yield). ^{1}H NMR (DMSO-d_6) δ 13.7 (br s, 1H), 8.76 (s, 1H), 8.23-8.14 (m, 3H), 8.10 (t, 2H), 7.83 (d, 1H), 7.68-7.62 (m, 3H), 7.43 (t, 2H); ES-MS (m/z) 357 $[M+1]^+$.

EXAMPLE 131

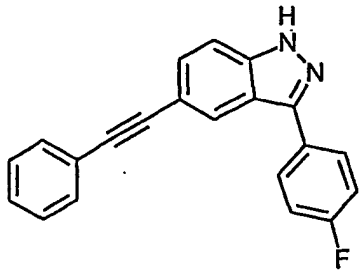
SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-2-METHYL-1,3,4-OXADIAZOLE



This was a byproduct isolated in the purification of Example 117, 5-[3-(4-fluorophenyl)(1H-indazole-5-yl)]-3-methyl-4H-1,2,4-triazole. ^{1}H NMR (DMSO-d_6) δ 13.6 (s, 1H), 8.55 (s, 1H), 8.0-8.08 (m, 3H), 7.8 (d, 1H), 7.4 (t, 2H), 2.5 (s, 3H), ES-MS (m/z) 295 $[M+1]^+$.

EXAMPLE 132

SYNTHESIS OF 3-(4-FLUOROPHENYL)-5-(2-PHENYLETHYNYL)-1H-INDAZOLE



A. 2-Amino-5-bromo-4'-fluorobenzophenone

To neat 4-fluorobenzoyl chloride (50.00 g, 315 mmol) in a flask at 130°C was added 4-bromoaniline (17.00 g, 100 mmol) in several portions. After it was stirred at 130°C for 1 hour and the temperature was raised to 190°C, to the reaction mixture was

added zinc chloride (11.00 g, 80.7 mmol) in several portions, then it was heated at 220°C for 22 hours. Once cooled to 180 °C, to the mixture was carefully added concentrated sulfuric acid (50 mL), acetic acid (70 mL), water (70 mL), and another portion of sulfuric acid (50 mL). The mixture was heated at 120°C overnight. It was poured into water (500 mL) and a white solid was precipitated. It was collected by filtration and was dissolved in ethyl acetate and washed with 5% sodium carbonate until pH of the aqueous phase reached 8. The filtrate was basified with sodium carbonate and extracted with ethyl acetate. The combined ethyl acetate layers were dried over magnesium sulfate, filtered, and concentrated. The residue was then purified by chromatography (SiO_2, 15-20% ethyl acetate/hexane) to provide the title compound (13.64 g, 46% yield). ^{1}H NMR ($CDCl_3$) δ 7.67 (m, 2H), 7.51 (d, 1H), 7.37 (dd, 1H), 7.14-7.20 (m, 2H), 6.65 (d, 1H), 6.02 (br s, 2H); ES-MS (m/z) 296 $[M+3]^+$, 294 $[M+1]^+$.

B. 5-Bromo-3-(4-fluorophenyl)-1H-indazole

To a solution of 2-amino-5-bromo-4'-fluorobenzophenone (13.50 g, 45.9 mmol) in 6 N hydrochloride solution (400 mL) and tetrahydrofuran (500 mL) at -15°C was slowly dropped a solution of sodium nitrite (4.12 g, 59.7 mmol) in water (20 mL). After stirring for 30 minutes in cold bath, to the reaction mixture was added a solution of tin(II) chloride dihydrate (28.48 g, 126 mmol) in concentrated hydrochloric acid (70 mL) dropwise. A white solid precipitated immediately. After 30 minutes, the white solid was filtered, dissolved in ethyl acetate, and washed with saturated sodium bicarbonate. The filtrate was neutralized with sodium hydroxide and extracted with dichloromethane. The ethyl acetate and dichloromethane layers were combined, dried over magnesium sulfate, and concentrated. Crystallization from ethyl acetate gave the title compound as a white solid (5.266 g). The mother liquor was then purified by chromatography (SiO_2, 15-30% ethyl acetate/hexane) to provide another batch of the title compound (3.429 g, total 8.695 g, 65% yield). ^{1}H NMR ($CDCl_3$) δ 10.54 (br s, 1H), 8.11 (m, 1H), 7.87-7.92 (m, 2H), 7.50 (m, 1H), 7.34 (d, 1H), 7.20-7.26 (m, 2H); ES-MS (m/z) 293 $[M+3]^+$, 291 $[M+1]^+$.

C. 5-Bromo-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole

To a solution of 5-bromo-3-(4-fluorophenyl)-1H-indazole (8.00 g, 27.48 mmol) in dried tetrahydrofuran (80 mL) under nitrogen at ambient temperature was added 3,4-dihydro-2H-pyran (5.78 g, 68.7 mmol) and p-toluenesulfonic acid monohydrate (1.00 g, 5.26 mmol). The reaction mixture was stirred at room temperature for 24 hours. It was quenched with dichloromethane and washed with 5% sodium carbonate and brine. The

dichloromethane layer was dried over magnesium sulfate and concentrated. Crystallization from diethyl ether and hexane provided the title compound (8.47 g, 82% yield). ^{1}H NMR ($CDCl_3$) δ 8.07 (t, 1H), 7.86-7.91 (m, 2H), 7.47-7.55 (m, 2H), 7.16-7.26 (m, 2H), 5.74 (dd, 1H), 4.05 (m, 1H), 3.76 (m, 1H), 2.60 (m, 1H), 2.08-2.21 (m, 2H), 1.66-1.83 (m, 3H); ES-MS (m/z) 377 $[M+3]^+$, 375 $[M+1]^+$.

D. 3-(4-Fluorophenyl)-5-(2-phenylethynyl)-1-(tetrahydropyran-2-yl)-1H-indazole

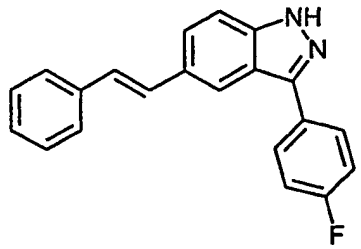
A mixture of 5-bromo-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole (0.375 g, 1.0 mmol), triethylamine (1.5 mL), tri-*o*-tolylphosphine (0.122 g, 0.4 mmol), tri(dibenzylideneacetone)dipalladium(0) (0.092 g, 0.1 mmol) and phenylacetylene (0.204 g, 2.0 mmol) in dried acetonitrile (10 mL) under nitrogen was heated to reflux overnight. It was quenched with water and extracted with ethyl acetate. The extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was then purified by chromatography (SiO_2, 10-15% ethyl acetate/hexane) to provide the title compound (0.127 g, 32% yield). ^{1}H NMR ($CDCl_3$) δ 8.16 (t, 1H), 7.93-7.97 (m, 2H), 7.54-7.64 (m, 4H), 7.34-7.37 (m, 3H), 7.21 (t, 2H) 5.77 (dd, 1H), 4.08 (m, 1H), 3.79 (m, 1H), 2.62 (m, 1H), 2.11-2.21 (m, 2H), 1.57-1.83 (m, 3H); ES-MS (m/z) 397 $[M+1]^+$.

E. 3-(4-Fluorophenyl)-5-(2-phenylethynyl)-1H-indazole

To a solution of 3-(4-fluorophenyl)-5-(2-phenylethynyl)-1-(tetrahydropyran-2-yl)-1H-indazole in tetrahydrofuran (15 mL) was added 6 N hydrochloride solution (10mL) and the mixture was stirred at ambient temperature overnight. After tetrahydrofuran was evaporated, the aqueous phase was neutralized with 5% sodium carbonate and extracted with ethyl acetate. The extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was then purified by chromatography (SiO_2, 15-30% ethyl acetate/hexane) to provide the title compound (0.071 g, 90% yield). ^{1}H NMR ($CDCl_3$) δ 10.19 (br, 1H), 8.20 (s, 1H), 7.94-7.98 (m, 2H), 7.55-7.61 (m, 3H), 7.48 (dd, 1H), 7.34-7.41 (m, 3H), 7.23 (t, 2H); ES-MS (m/z) 313 $[M+1]^+$.

EXAMPLE 133

SYNTHESIS OF 5-[(1E)-2-PHENYLVINYL]-3-(4-FLUOROPHENYL)-1H-INDAZOLE



A. 5-[(1E)-2-Phenylvinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole

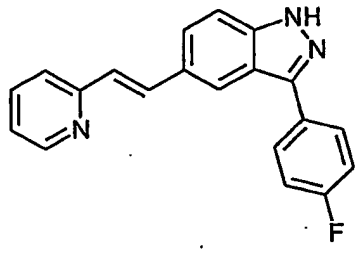
The title compound was prepared as described in Example 132 D, using styrene (0.208 g, 2.0 mmol) (0.267 g, 67% yield). ^{1}H NMR ($CDCl_3$) δ 7.94-7.99 (M, 3H), 7.69 (dd, 1H), 7.62 (d, 1H), 7.55 (d, 1H), 7.53 (d, 1H), 7.37 (t, 2H), 7.19-7.29 (M, 4H), 7.15 (d, 1H), 5.77 (dd, 1H), 4.08 (m, 1H), 3.79 (m, 1H), 2.63 (m, 1H), 1.83-2.21 (m, 2H), 1.57-1.80 (m, 3H); ES-MS (m/z) 399 $[M+1]^+$.

B. 5-[(1E)-2-Phenylvinyl]-3-(4-fluorophenyl)-1H-indazole

The title compound was prepared as described in Example 132.E, using 5-[(1 E)-2-phenylvinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole (0.20 g, 0.5 mmol) (0.124 g, 79% yield). ^{1}H NMR ($CDCl_3$) δ 10.1 (br 5, 1H), 7.95-8.02 (m, 3H), 7.72 (dd, 1H), 7.49-7.56 (m, 3H), 7.38 (t, 2H), 7.21-7.30 (m, 4H), 7.15 (d, 1H); ES-MS (m/z) 315 $[M+1]^+$.

EXAMPLE 134

SYNTHESIS OF 5-[(1E)-2-(2-PYRIDYL)VINYL]-3-(4-FLUOROPHENYL)-1H-INDAZOLE



A. 5-[(1E)-2-Pyridylvinyl]1-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole

The title compound was prepared as described in Example 132.D, using 2-

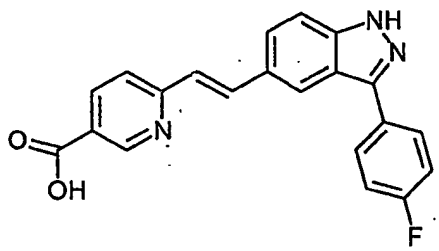
vinylpyridine (0.210 g, 2.0 mmol) (0.305 g, 76% yield). ^{1}H NMR ($CDCl_3$) δ 8.61 (d, 1H), 8.09 (d, 1H), 7.94-7.98 (m, 2H), 7.62-7.80 (m, 4H), 7.42 (d,1H), 7.13-7.24 (m, 4H), 5.77 (dd, 1H), 4.08 (m, 1H), 3.79 (m, 1H), 2.63 (m, 1H), 2.10-2.21 (m, 2H), 1.64-1.83 (m, 3H); ES-MS (m/z) 400 $[M+1]^+$.

B. 5-[(1E)-2-Pyridylvinyl]-3-(4-fluorophenyl)-1H-indazole

The title compound was prepared as described in Example 132 E, using 5-[(1 E)-2-pyridylvinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole (0.20 g, 0.5 mmol) (0.149 g, 94% yield). ^{1}H NMR (DMSO-d_6) δ 13.4 (br s, 1H), 8.76 (d, 1H), 8.53 (t, 1H), 8.35-8.45 (m, 3H), 8.06 (m, 2H), 7.70-7.85 (m, 4H), 7.40 (m, 2H); ES-MS (m/z) 316 $[M+1]^+$.

EXAMPLE 135

SYNTHESIS OF 4-{(1 E)-2-[(3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]VINYL} BENZOIC ACID



A. 4-{(1E)-2-[(3-(4-Fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]vinyl}benzoic Acid

The title compound was prepared as described in Example 132 D, using 4-vinylbenzoic acid (0.296 g, 2.0 mmol) (0.284 g, 64% yield). ^{1}H NMR (DMSO-d_6) δ 12.87 (br s, 1H), 8.25 (s, 1H), 8.07 (m, 2H), 7.94 (m, 3H), 7.84 (d, 1H), 7.74 (d, 2H), 7.63 (d, 1H), 7.40 (m, 3H), 5.94 (d, 1H), 3.92 (m, 1H), 3.81 (m, 1H), 2.47 (m, 1H), 2.06 (m, 2H), 1.78 (m, 3H); ES-MS (m/z) 443 $[M+1]^+$.

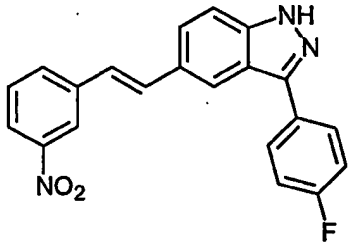
B. 4-{(1E)-2-[(3-(4-Fluorophenyl)-1H-indazol-5-yl]vinyl}benzoic Acid

The title compound (0.163 g, 91% yield) was prepared as described in Example 132 E, using 4-{(1 E)-2-[(3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole-5-yl]vinyl}benzoic acid (0.221 g, 0.5 mmol). ^{1}H (DMSO-d_6) δ 13.35 (br s, 1H),

12.8 (br s, 1H), 8.25 (s, 1H), 8.08 (m, 2H), 7.95 (d, 2H), 7.83 (d, 1H), 7.74 (d, 2H), 7.63 (m, 2H), 7.38 (m, 3H); ES-MS (m/z) 359 $[M+1]^+$.

EXAMPLE 136

SYNTHESIS OF 5-[(1E)-2-(3-NITROPHENYL)VINYL]-3-(4-FLUOROPHENYL) -1H-INDAZOLE

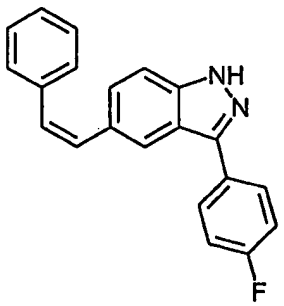


A. 5-[(1E)-2-(3-Nitrophenyl)vinyl]-3-(4-fluorophenyl)-1H-indazole

The title compound (0.134 g, 52% yield) was prepared as described in Example 132 D, using 5-bromo-3-(4-fluorophenyl)-1H-indazole (0.291 g, 1.0 mmol) and 3-nitrostyrene (0.298 g, 2.0 mmol). ^{1}H NMR ($CDCl_3$) δ 10.12 (br s, 1H), 8.41 (t, 1H), 8.11 (ddd, 1H), 8.07 (s, 1H), 7.97 (m, 2H), 7.82 (d, 1H), 7.73 (dd, 1H), 7.54 (m, 2H), 7.40 (d, 1H), 7.26 (m, 2H), 7.16 (d, 1H); ES-MS (m/z) 360 $[M+1]^+$.

EXAMPLE 137

SYNTHESIS OF 5-[(1Z)-2-PHENYLVINYL]-3-(4-FLUOROPHENYL)-1H-INDAZOLE



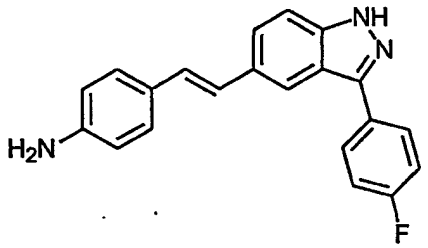
A. 5-[(1Z)-2-Phenylvinyl]-3-(4-fluorophenyl)-1H-indazole

A mixture of 3-(4-fluorophenyl)-5-(2-phenylethynyl)-1H-indazole (0.050 g, 0.16 mmol), quinoline (0.030 g), and palladium (5 wt. % on barium carbonate, 0.015 g) in ethyl acetate (10 mL) was stirred under hydrogen for 5 hours. It was filtered with celite and

washed with ethyl acetate. The filtrate was washed with 5% hydrochloric acid solution and brine, dried over magnesium sulfate, filtered, and concentrated. The residue was then purified by chromatography (SiO_2, 15-30% ethyl acetate/hexane) and by HPLC to provide the title compound (0.023 g, 46% yield): ^{1}H NMR ($CDCl_3$) δ 10.15 (br s, 1H), 7.83 (s, 1H), 7.70 (m, 2H), 7.29 (m, 7H), 7.11 (t, 2H), 6.72 (d, 1H), 6.68 (d, 1H); ES-MS (m/z) 315 $[M+1]^+$.

EXAMPLE 138

SYNTHESIS OF 5-[(1E)-2-(4-AMINOPHENYL)VINYL]-3-(4-FLUOROPHENYL)-1H-INDAZOLE



A. 5-[(1E)-2-(4-Aminophenyl)vinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole

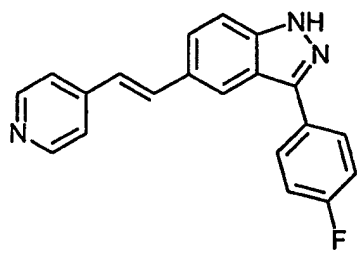
The title compound was prepared as described in Example 132 D, using 4-vinylaniline (0.286 g, 2.4 mmol) (0.196 g, 49% yield): ^{1}H NMR ($CDCl_3$) δ 7.96 (m, 2H), 7.92 (s, 1H), 7.5 (ddd, 1H), 7.59 (d, 1H), 7.36 (d, 2H), 7.21 (t, 2H), 7.05 (d, 1H), 7.04 (d, 1H), 6.69 (m, 2H), 5.76 (dd, 1H), 4.08 (m, 1H), 3.78 (m, 1H), 3.7 (br, 2H), 2.63 (m, 1H), 2.14 (m, 2H), 1.79 (m, 3H); ES-MS (m/z) 414 $[M+1]^+$.

B. 5-[(1E)-2-(4-Aminophenyl)vinyl]-3-(4-fluorophenyl)-1H-indazole

The title compound was prepared as described in Example 132 E, using 5-[(1E)-2-(4-aminophenyl)vinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole (0.185 g, 0.45 mmol) (0.094 g, 64% yield): ^{1}H NMR ($CDCl_3$) δ 10.1 (br s, 1H), 7.97 (m, 3H), 7.66 (dd, 1H), 7.47 (dd, 1H), 7.37 (m, 2H), 7.23 (m, 2H), 7.05 (m, 2H), 6.71 (m, 2H); ES-MS (m/z) 330 $[M+1]^+$.

EXAMPLE 139

SYNTHESIS OF 5-[(1 E)-2-(4-PYRIDYL)VINYL]-3-(4-FLUOROPHENYL)-1H-INDAZOLE



A. 5-[(1E)-2-(4-Pyridyl)vinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole

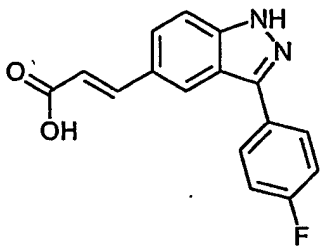
The title compound (0.284 g, 74% yield) was prepared as described in Example 132 D, using 4- vinylpyridine (0.252 g, 2.4 mmol) (0.284 g, 74% yield). ^{1}H NMR ($CDCl_3$) δ 8.58 (dd, 2H), 7.95 (m, 3H), 7.69 (dd, 1H), 7.65 (d, 1H), 7.44 (d, 1H), 7.39 (dd, 2H), 7.22 (m, 2H), 7.04 (d, 1H), 5.78 (dd, 1H), 4.09 (m, 1H), 3.80 (m, 1H), 2.63 (m, 1H), 2.15 (m, 2H), 1.80 (m, 3H); ES-MS (m/z) 400 $[M+1]^+$.

B. 5-[(1E)-2-(4-Pyridyl)vinyl]-3-(4-fluorophenyl)-1H-indazole

The title compound (0.164 g, 79% yield) was prepared as described in Example 132 E, using 5-[(1 E)-2-(4-pyridyl)vinyl]-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole (0.265 g, 0.66 mmol). ^{1}H NMR ($CDCl_3$) δ 10.3 (br s, 1H), 8.59 (d, 2H), 8.06 (s, 1H), 7.96 (dd, 2H), 7.72 (dd, 1H), 7.54 (d, 1H), 7.46 (d, 1H), 7.40 (d, 2H), 7.25 (t, 2H), 7.04 (d, 1H); ES-MS (m/z) 416 $[M+1]^+$.

EXAMPLE 140

SYNTHESIS OF (2E)-3-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]PROP-2-ENOIC ACID



A. Ethyl(2E)-3-[3-(4-Fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]prop-2-enoate

The title compound (0.881 g, 74% yield) was prepared as described in Example 132 D, using ethyl acrylate (0.751 g, 7.5 mmol). ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.92 (m, 2H), 7.83 (d, 1H), 7.64 (d, 2H), 7.21 (t, 2H), 6.46 (d, 1H), 5.76 (dd, 1H), 4.28 (q, 2H), 4.07 (m, 1H), 3.78 (m, 1H), 2.63 (m, 1H), 2.14 (m, 2H), 1.76 (m, 3H), 1.35 (t, 3H); ES-MS (m/z) 395 $[M+1]^+$.

B. Ethyl (2E)-3-[3-(4-Fluorophenyl)-1H-indazol-5-yl]prop-2-enoate

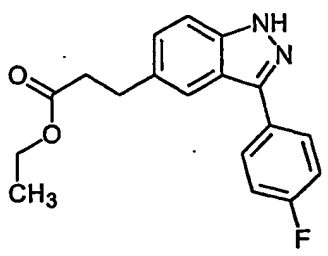
The title compound (0.602 g, 90% yield) was prepared as described in Example 132 E, using ethyl (2E)-3-[3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]prop-2-enoate (0.850 g, 2.15 mmol). ^{1}H NMR ($CDCl_3$) δ 10.51 (br s, 1H), 8.09 (s; 1H), 7.93 (m, 2H), 7.84 (d, 1H), 7.65 (d, 1H), 7.49 (d, 1H), 7.24 (t, 2H), 6.47 (d, 1H), 4.29 (q, 2H), 1.36 (t, 3H); ES-MS (m/z) 311 $[M+1]^+$.

C. (2E)-3-[3-(4-Fluorophenyl)-1H-indazol-5-yl]prop-2-enoic Acid

To a solution of ethyl (2E)-3-[3-(4-fluorophenyl)-1H-indazol-5-yl]prop-2-enoate (0.10 g, 0.32 mmol) in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide (0.032 mg, 1.6 mmol) in water (5 mL) and the mixture was stirred at ambient temperature overnight. The reaction mixture was acidified with 6 N hydrochloric acid solution to give a white solid. It was then purified by HPLC to provide the title compound (0.43 g, 48% yield): ^{1}H NMR (DMSO-d_6) δ 13.45 (br s, 1H), 12.28 (br s, 1H), 8.39 (s, 1H), 8.11 (d, 1H), 8.10 (d, 1H), 7.83 (d, 1H), 7.79 (d, 1H), 7.60 (d, 1H), 7.35 (t, 2H), 6.57 (d, 1H); ES-MS (m/z) 283 $[M+1]^+$.

EXAMPLE 141

SYNTHESIS OF ETHYL (2E)-3-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]PROP-2-ENOATE

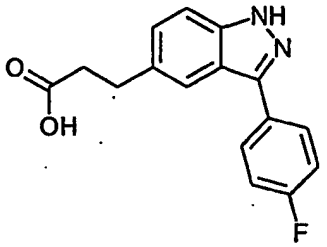


A. Ethyl(2E)-3-[3-(4-Fluorophenyl)-1H-indazol-5-yl]prop-2-enoate

A suspension of ethyl (2E)-3-[3-(4-fluorophenyl)-1H-indazol-5-yl]prop-2-enoate (0.48 g, 1.54 mmol) and palladium (10 wt % on activated carbon, 0.05 g) in ethyl acetate (15 mL) was stirred under hydrogen for 6 hours. It was filtered with celite, washed with ethyl acetate, and concentrated. The residue was then purified by chromatography (SiO_2, 30-50% ethyl acetate/hexane) to provide the title compound (0.465 g, 96% yield): ^1H NMR ($CDCl_3$) δ 10.28 (br s, 1H), 7.92 (m, 2H), 7.78 (s, 1H), 7.42 (d, 1H), 7.29 (d,1H), 7.21 (t, 2H), 4.13 (q, 2H), 3.10 (t, 2H), 2.69 (t, 2H), 1.23 (t, 3H); ES-MS (m/z) 313 $[M+1]^+$.

EXAMPLE 142

SYNTHESIS OF 3-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]PROPANOIC ACID

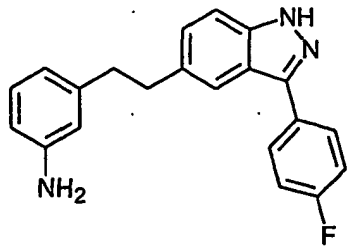


A. 3-[3-(4-Fluorophenyl)-1H-indazol-5-yl]propanoic Acid

The title compound (0.224 g, 62% yield) was prepared as described in Example 140 C, using ethyl (2E)-3-[3-(4-fluorophenyl)-1H-indazol-5-yl]prop-2-enoate (0.4C g, 1.28 mmol). ^1H NMR ($CDCl_3$) δ 13.15 (br s, 1H), 8.01 (m, 2H), 7.78 (s, 1H), 7.50 (d, 1H), 7.33 (m, 3H), 2.96 (t, 2H), 2.60 (t, 2H); ES-MS (m/z) 285 $[M+1]^+$.

EXAMPLE 143

SYNTHESIS OF 5-[2-(3-AMINOPHENYL)ETHYL]-3-(4-FLUOROPHENYL)-1H-INDAZOLE

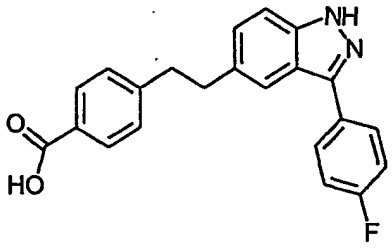


A. 5-[2-(3-Aminophenyl)ethyl]-3-(4-fluorophenyl)-1H-indazole

The title compound (0.051 g, 55% yield) was prepared as described in Example 141 A, using 5-[(1 E)-2-(3-Nitrophenyl)vinyl]-3-(4-fluorophenyl)-1H-indazole (0.10 g, 2.78 mmol). ^{1}H NMR ($CDCl_3$) δ 9.8 (br s, 1H), 7.88 (m, 2H), 7.69 (s, 1H), 7.43 (d, 1H), 7.18-7.26 (m, 3H), 7.09 (t, 1H), 6.62 (d, 1H), 6.54 (m, 2H), 3.5 (br s, 2H), 3.05 (m, 2H), 2.88 (m, 2H); ES-MS (m/z) 332 $[M+1]^+$.

EXAMPLE 144

SYNTHESIS OF 4-{2-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]ETHYL} BENZOIC ACID

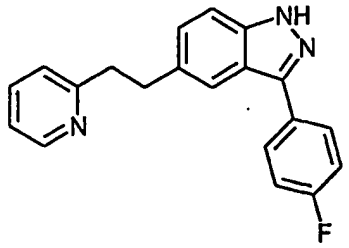


A. 4-{2-[3-(4-Fluorophenyl)-1H-indazol-5-yl]ethyl}benzoic Acid

The title compound (0.044 g, 36% yield) was prepared as described in Example 141 A, using 4-{(1 E)-2-[(3-(4-fluorophenyl)-1H-indazol-5-yl]vinyl}benzoic acid (0.120 g, 0.33 mmol) in methanol and it was then purified by HPLC. ^{1}H NMR (DMSO-d_6) δ 13.13 (br s, 1H), 7.76-7.94 (m, 5H), 7.48 (m, 1H), 7.32 (m, 5H), 3.03 (m, 4H); ES-MS (m/z) 361 $[M+1]^+$.

EXAMPLE 145

SYNTHESIS OF 3-(4-FLUOROPHENYL)-5-[2-(2-PYRIDYL)ETHYL]-1H-INDAZOLE

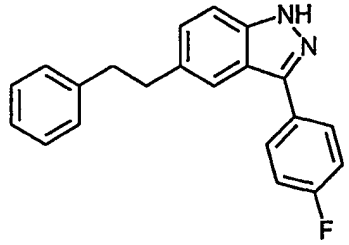


A. 3-(4-Fluorophenyl)-5-[2-(2-pyridyl)ethyl]-1H-indazole

The title compound was prepared as described in Example 141 A, using 5-[(1 E)-2-pyridylvinyl]-3-(4-fluorophenyl)-1H-indazole (0.125 g, 0.4 mmol) in methanol and it was then purified by HPLC (0.060 g, 47% yield): ^{1}H NMR (DMSO-d_6) δ 13.14 (br s, 1H), 8.52 (d, 1H), 7.95 (m, 2H), 7.79 (s, 1H), 7.69 (ddd, 1H), 7.42 (dd, 1H), 7.22-7.35 (m, 5H), 3.12 (m, 4H); ES-MS (m/z) 318 $[M+1]^+$.

EXAMPLE 146

SYNTHESIS OF 3-(4-FLUOROPHENYL)-5-(2-PHENYLETHYL)-1H-INDAZOLE

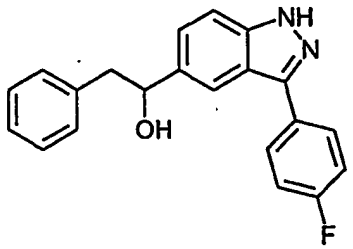


A. 3-(4-Fluorophenyl)-5-(2-phenylethyl)-1H-indazole

The title compound (0.035 g, 35% yield) was prepared as described in Example 141 A, using 5-[(1 E)-2-phenylvinyl]-3-(4-fluorophenyl)-1H-indazole (0.10 g, 0.32 mmol). ^{1}H NMR ($CDCl_3$) δ 10.0 (br s, 1H), 7.87 (m, 2H), 5 7.66 (m, 1H), 7.43 (dd, 1H), 7.27-7.30 (m, 3H), 7.17-7.24 (m, 5H), 3.08 (m, 2H), 2.98 (m, 2H); ES-MS (m/z) 317 $[M+1]^+$.

EXAMPLE 147

SYNTHESIS OF 1-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-2-PHENYLETHAN-1-OL



A. 1-[3-(4-Fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]-2-phenylethan-1-ol

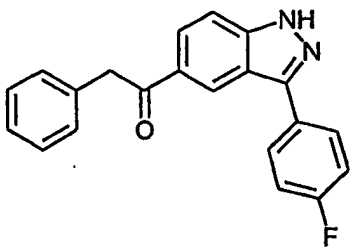
To a solution of 5-bromo-3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazole (0.50 g, 1.0 mmol) in dried tetrahydrofuran (15 mL) under nitrogen at -78°C was added dropwise a 1.6 M solution of butyl lithium in hexane (1.1 mL, 1.7 mmol). After stirring for 20 minutes, to the reaction mixture was added phenylacetaldehyde (0.228 g, 1.9 mmol). The reaction mixture was stirred additional 1 hour at -78°C and the temperature was gradually raised to room temperature. It was quenched with water and extracted with dichloromethane. The extracts were dried over magnesium sulfate, filtered, and concentrated. The residue was then purified by chromatography (SiO_2, 15-30% ethyl acetate/hexane) to provide the title compound (0.246 g, 44% yield): ^{1}H NMR ($CDCl_3$) δ 7.86 (m, 2H), 7.80 (d, 1H), 7.09-7.47 (m, 9H), 6.98 (dd, 1H), 5.70 (dd, 1H), 5.07 (t, 1H), 4.08 (m, 1H), 3.65 (m, 1H), 3.06 (d, 1H), 2.67 (m, 2H), 2.11 (m, 2H), 1.75 (m, 3H); ES-MS (m/z) 417 $[M+1]^+$.

B. 1-[3-(4-Fluorophenyl)-1H-indazol-5-yl]-2-phenylethan-1-ol

The title compound was prepared as described in Example 132 E, using 1-[3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]-2-phenylethan-1-ol (0.130 g, 0.31 mmol) to provide the title compound (0.024 g, 23% yield): ^{1}H NMR ($CDCl_3$) δ 10.0 (br s, 1H), 7.89 (m, 2H), 7.49 (m, 1H), 7.40 (dd, 1H), 7.27-7.34 (m, 3H), 7.16-7.23 (m, 5H), 7.05 (dd, 1H), 5.07 (dd, 1H), 3.09 (m, 2H); ES-MS (m/z) 333 $[M+1]^+$.

EXAMPLE 148

SYNTHESIS OF 1-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-2-PHENYLETHAN-1-ONE



A. 1-[3-(4-Fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]-2-phenylethan-1-one

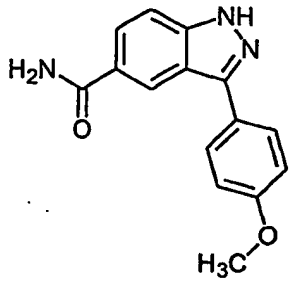
A suspension of 1-[3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]-2-phenylethan-1-ol (0.223 g, 0.54 mmol) and pyridinium chlorochromate (1.0 g, 4.6 mmol) in dried dichloromethane (10 mL) under nitrogen was stirred at ambient temperature for 6 hours. It was diluted with dichloromethane and washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was then purified by chromatography (SiO_2, 15-30% ethyl acetate/hexane) to provide the title compound (0.112 g, 51% yield): ^{1}H NMR ($CDCl_3$) δ 8.62 (d, 1H), 8.10 (dd, 1H), 7.85-7.90 (m, 2H), 7.65 (dd, 1H), 7.19-7.37 (m, 7H), 5.77 (dd, 1H), 4.35 (s, 2H), 4.06 (m, 1H), 3.77 (m, 1H), 2.59 (m, 1H), 2.14 (m, 2H), 1.70 (m, 3H); ES-MS (m/z) 415 $[M+1]^+$.

B. 1 -[3-(4-Fluorophenyl)-1H-indazol-5-yl]-2-phenylethan-1-one

The title compound (0.021 g, 27% yield) was prepared as described in Example 132 E, using 1-[3-(4-fluorophenyl)-1-(tetrahydropyran-2-yl)-1H-indazol-5-yl]-2-phenylethan-1-one (0.10 g, 0.24 mmol. ^{1}H NMR ($CDCl_3$) δ 10.37 (br s, 1H), 8.67 (d, 1H), 8.12 (dd, 1H), 7.86-7.91 (m, 2H), 7.52 (d, 1H), 7.21-7.38 (m, 7H), 4.37 (s, 2H), 3.09 (m, 2H); ES-MS (m/z) 331 $[M+1]^+$.

EXAMPLE 149

SYNTHESIS OF 3-(4-METHOXYPHENYL)-1H-INDAZOLE-5-CARBOXAMIDE



A. 1H-Indazole-5-carbonitrile

To a 1-L beaker was added 20.0 g (150 mmol) of 5-aminoindazole, and 150 g of ice. The mixture was stirred with a magnetic stir bar and cooled on an ice-water bath. To this mixture was added 37.5 mL of concentrated aqueous hydrochloric acid, followed by a solution of 10.5 g (152 mmol, 1.01 equiv.) of sodium nitrite in 30 mL of H_2O, dropwise over 15 min. The mixture was vigorously stirred for 30 min. and then carefully neutralized to pH ca. 7.0 with 9.5 g of solid sodium carbonate (Na_2CO_3). This mixture was transferred to a 1-L separatory funnel, kept cold by the addition of ice, and added dropwise to an ice cooled, magnetically stirred mixture of 16.8 g (188 mmol, 1.24 equiv.) of copper (I) cyanide (CuCN), 24.4 g (498 mmol, 3.32 equiv.) of sodium cyanide (NaCN), 112 mL H_2O, and 250 mL of ethyl acetate (EtOAc) in a 2-L erlenmeyer flask over 20 min. Nitrogen gas was evolved from the reaction. The mixture turned dark quickly, and was stirred on ice for 30 min. and then the ice was removed. Stirring was continued for 3.5 h. The mixture was then heated on a hot plate until the internal temperature was 50°C. The reaction was removed from the hot plate and allowed to cool to 35°C, and filtered through filter paper. The layers were separated, and the organic layer was washed with saturated aqueous NaCl, and dried (Na_2SO_4). The organic layer was poured directly onto a 65 mm column containing 200 g of silica gel and eluted with EtOAc. Fractions of 500 mL were collected, and all product containing fractions were combined and concentrated to give the title compound (19.60 g, 91% yield): ES-MS (m/z) 144 $[M+1]^+$.

B. 3-Bromo-1H-indazole-5-carbonitrile

A 2-L round bottomed flask was charged with 1H-indazole-5-carbonitrile (17.6 g, 123 mmol), 333 mL methanol (MeOH), 333 mL of 2.0 M aq. NaOH, and a solution of bromine (Br_2, 54.7 g, 344 mmol, 2.80 equiv.) in 166 mL of 2.0 M aq. NaOH. The

mixture was warmed on an oil bath to 40°C (external temperature) for 6 h, and then cooled to room temperature in a water bath. The pH of the solution adjusted to ca. 5.5 with 103 mL of 4.0 M aq. HCl. The resulting precipitate was collected by filtration, washed with 200 mL of H_2O, and dried. The product was purified by chromatography on 265 g of silica gel using 30-40% EtOAc in hexanes. This afforded the title compound (12.83 g, 47% yield): ES-MS (m/z) 222 $[M+1]^+$.

C. 3-Bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

To a solution of 13.67 g (61.56 mmol) of 3-bromo-1H-indazole-5-carbonitrile and 2.06 g (10.8 mmol, 0.175 equiv.) of p-toluenesulfonic acid monohydrate in 247 mL of anhydrous tetrahydrofuran (THF) was added 11.2 mL (123 mmol, 2.00 equiv.) of 3,4-dihydro-2H-pyran. The mixture was refluxed under a nitrogen atmosphere for 14h. The reaction was quenched with saturated aqueous sodium bicarbonate (sat. aq. $NaHCO_3$). The mixture was extracted twice with EtOAc. The combined organics were washed with 2 x sat. aq. $NaHCO_3$, 1 x sat. aq. NaCl, and dried over Na_2SO_4. Chromatography of the crude material on 200 g of silica gel using 30% EtOAc in hexanes afforded the title compound (14.34 g, 76% yield): ES-MS (m/z) 306 $[M+1]^+$.

D. 3-(4-Methoxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

A flask was charged with 300 mg (0.98 mmol) of 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile, 223 mg (1.47 mmol, 1.50 equiv.) of 4-methoxyphenylboronic acid, 80.3 mg (0.098 mmol, 0.100 equiv.) of [1,1'-bis (diphenylphosphino)-ferrocene} dichloropalladiuin (II) complex with dichloromethane (Aldrich), 1.04 g (4.90 mmol, 4.98 equiv.) of powdered potassium phosphate (K_3PO_4), and 4.90 mL of anhydrous 1,2-dimethoxyethane (DME). The mixture was refluxed under nitrogen for 19 h. The mixture was diluted with CH_2Cl_2, washed with 2 x sat. aq. $NaHCO_3$, and dried (Na_2SO_4). The crude material was purified by silica gel chromatography using 20-30% EtOAc in hexanes affording the title compound (251 mg, 77% yield): ES-MS (m/z) 334 $[M+1]^+$.

E. 3-(4-Methoxyphenyl)-1H-indazole-5-carbonitrile

A mixture of 251 mg (0.753 mmol) of 3-(4-methoxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile, 5.0 mL of dioxane, and 5.0 mL of 6.0 N aq. HCl was heated at 65°C for 22 h. The reaction mixture was added to a mixture of 10.0 mL of H_2O and 20.0 mL of EtOAc with stirring. The layers were separated and the aqueous layer was

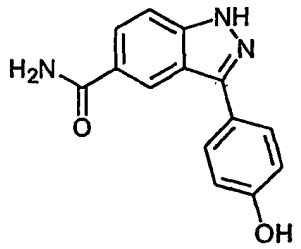
extracted with EtOAc. The combined organic layers were added to 60 mL of sat. aq. $NaHCO_3$ with rapid stirring. The layers were separated, and the organic layer was washed with sat. aq. $NaHCO_3$, and dried (Na_2SO_4). Purification of the crude material by silica gel chromatography using 30 - 50% EtOAc in hexanes afforded the title compound (129 mg, 71% yield): ES-MS (m/z) 250 $[M+1]^+$.

F. 3-(4-Methoxyphenyl)-1H-indazole-5-carboxamide

A mixture of 20 mg (0.080 mmol) of 3-(4-methoxyphenyl)-1H-indazole-5-carbonitrile, 0.428 mL of 95% denatured ethanol, 0.021 mL of H_20, 0.32 mL of 30% aqueous hydrogen peroxide (aq. H_20_2) and 0.032 mL of 6.0 N aq. NaOH (0.192 mmol, 2.4 equiv.) was heated at 50°C for 3 h, and then acidified to pH = 6.0 with 0.052 mL of 6.0 N 10 aq. HCl. The mixture was extracted with 2 x EtOAc. The combined organics were washed with 2 x sat. aq. $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated affording the title compound (8.9 mg, 41.6% yield): ^1H NMR ($CDCl_3$/DMSO-d_6) δ 12.5 (br s, 1H), 8.60 (s, 1H), 7.95 (d, 2H), 7.85 (d, 2H), 7.55 (d, 1H), 7.05 (d, 2H), 3.89 (s, 3H); ES-MS (m/z) 268 $[M+1]^+$.

EXAMPLE 150

SYNTHESIS OF 3-(4-HYDROXYPHENYL)-1H-INDAZOLE-5-CARBOXAMIDE



A. 3-(4-Hydroxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound (219 mg, 57% yield) was prepared as described in Example 149 D using 4-hydroxybenzeneboronic acid (250 mg, 1.81 mmol). ES-MS (m/z) 320 $[M+l]^+$.

B. 3-(4-Hydroxyphenyl)-1H-indazole-5-carbonitrile

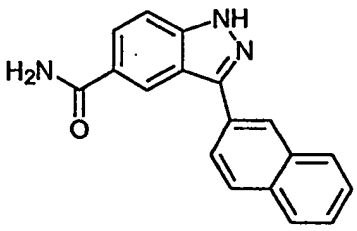
The title compound (520 mg, 82% yield) was prepared as described in Example 149.E using 3-(4-hydroxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (860 mg, 2.69 mmol). ES-MS (m/z) 236 $[M+1]^+$.

C. 3-(4-Hydroxyphenyl)-1H-indazole-5-carboxainide

The title compound (30 mg, 48% yield) was prepared as described in Example 149 F using 3-(4-hydroxyphenyl)-1H-indazole-5-carbonitrile (60 mg, 0.255 mmol). ^{1}H NMR (DMSO-d_6) δ 13.22 (s, 1H), 9.67 (s, 1H), 8.56 (s, 1H), 8.1 (br s, 1H), 7.95-7.80 (m, 3H), 7.56 (d, 1H), 7.4 (br, 1H), 6.93 (d, 2H); ES-MS (m/z) 254 $[M+1]^+$.

EXAMPLE 151

SYNTHESIS OF 3-(2-NAPHTHYL)-1H-INDAZOLE-5-CARBOXAMIDE



A. 3-(2-Naphthyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound (262 mg, 76% yield) was prepared as described in Example 149 D using 2-naphthaleneboronic acid (252 mg, 1.46 mmol. ES-MS (m/z) 354 $[M+1]^+$.

B. 3-(2-Naphthyl)-1H-indazole-5-carbonitrile

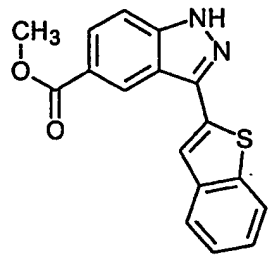
The title compound (105 mg, 53% yield) was prepared as described in Example 149 E using 3-(2-naphthyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (262 mg, 0.741 mmol). ES-MS (m/z) 270 $[M+1]^+$.

C. 3-(2-Naphthyl)-1H-indazole-5-carboxamide

The title compound (142 mg, 79% yield) was prepared as described in Example 149 F using 3-(2-naphthyl)-1H-indazole-5-carbonitrile (168 mg, 0.624 mmol). ^{1}H NMR (DMSO-d_6) δ 13.53 (s, 1H), 8.77 (s, 1H), 8.60 (s, 1H), 8.23 (dd, 2H), 8.16-8.05 (m, 2H), 7.98 (m, 2H), 7.68-7.52 (m, 3H), 7.39 (br s, 1H); ES-MS (m/z) 288 $[M+1]^+$.

EXAMPLE 152

SYNTHESIS OF METHYL 3-BENZO[B]THIOPHEN-2-YL-1H-INDAZOLE-5-CARBOXYLATE



A. 3-Bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carboxamide

The title compound was prepared as described in Example 149 F using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (1.50 g, 4.92 mmol) to provide the title compound (1.37 g, 86% yield): ES-MS (m/z) 324 $[M+1]^+$.

B. 3-Benzo[b]thiophen-2-yl-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carboxamide

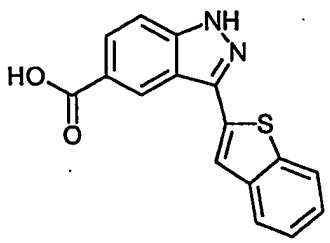
A mixture of 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carboxamide (425 mg, 1.31 mmol), benzo[b]thiophene-2-boronic acid (348 mg, 1.95 mmol, 1.49 equiv.), [1,1'-bis(diphenylphosphino)-ferrocene} dichloropalladium (II) complex with dichloromethane (107 mg, 0.131 mmol, 0.10 equiv.), potassium phosphate (K_3PO_4, 1.38 g, 6.50 mmol, 4.96 equiv.) and 6.5 mL of DME were refluxed for 18 h and concentrated. Purification by silica gel chromatography using 0-5% MeOH in EtOAc as eluent afforded the title compound (126 mg, 26% yield): ES-MS (m/z) 378 $[M+1]^+$.

C. Methyl 3-benzo[b]thiophen-2-yl-1H-indazole-5-carboxylate

A mixture of 3-benzo[b]thiophen-2-yl-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carboxamide (126 mg, 0.334 mmol), 10.0 mL of MeOH, and 10.0 mL of 6.0 N aq. HCl were heated at 65°C for 24 h. The reaction mixture was added dropwise to 50 mL of 6.0 N aq. NaOH with stirring. This mixture was extracted with 3 x EtOAc and the combined organics were dried (Na_2SO_4). Purification by silica gel chromatography using 30-40% EtOAc in hexanes afforded the title compound (27.0 mg, 26% yield): ^1H NMR (DMSO-d_6) δ 13.75 (br s, 1H), 8.84 (s, 1H), 8.19 (s, 1H), 8.15-7.95 (m, 3H), 7.74 (d, 1H), 7.45-7.35 (m, 2H), 3.94 (s, 3H); ES-MS (m/z) 378 $[M+1]^+$.

EXAMPLE 153

SYNTHESIS OF 3-BENZO[B]THIOPHEN-2-YL-1H-INDAZOLE-5-CARBOXYLIC ACID

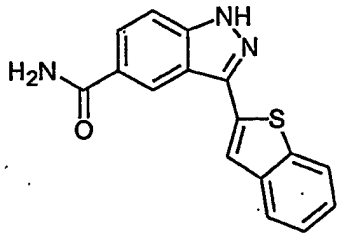


A. 3-Benzo[b]thiophen-2-yl-1H-indazole-5-carboxylic acid

A solution of methyl 3-benzo[b]thiophen-3-yl-1H-indazole-5-carboxylate (20 mg, 0.065 mmol), 5.00 mL of MeOH, and 5.00 mL of 6.0 N aq. NaOH was heated at 85°C for 2.5 h. The mixture was diluted with 6.0 N aq. NaOH, and extracted with 3 x EtOAc. The aqueous layer was then acidified to pH = 1.0 with 6.0 N aq. HCl. This mixture was extracted with 3 x EtOAc, and the combined organics were dried (Na_2SO_4), filtered, and concentrated to give the title compound (5 mg, 26% yield): ^{1}H NMR (DMSO-d_6) δ 13.71 (br s, 1H), 13.0 (very br s, 1H), 8.83 (s, 1H), 8.17 (s, 1H), 8.05-7.95 (m, 3H), 7.70 (d, 2H), 8.50-8.35 (m, 2H); ES-MS (m/z) 295 $[M+1]^+$.

EXAMPLE 154

SYNTHESIS OF 3-BENZO[B]THIOPHEN-2-YL-1H-INDAZOLE-5-CARBOXAMIDE



A. 3-Benzo[b]thiophen-2-yl-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound (397 mg, 110% yield, 85.5% pure by HPLC) was prepared as described in Example 149 D using benzo[b]thiophene-2-boronic acid (348 mg, 1.95 mmol). ES-MS (m/z) 360 $[M+1]^+$.

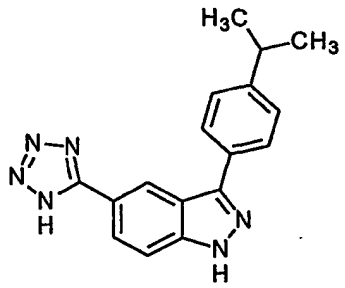
mmol), and potassium phosphate (1.03 g, 4.9 mmol) (0.097 g, 32 % yield): ES-MS (m/z) 310 $[M+1]^+$.

B. 2-(5-(2H-1,2,3,4-Tetrazo-5-yl)-1H-indazol-3-yl)thiophene

The title compound was prepared from 1-perhydro-2H-pyran-2-yl-3-(2-thienyl)-1H-indazole-5-carbonitrile (0.095 g, 0.307 mmol), azidotributyl tin (0.112 g, 0.093 mL, 0.338 mmol) in toluene (10 mL) as described for the preparation of Example 167. Deprotection was effected by treating a dioxane solution (5 mL) with 8 mL of 4.0 N solution of hydrogen chloride in 1,4-dioxane. The compound was purified by preparative HPLC (10-100% acetonitrile in H_2O, 20 min) (0.004 g, 0.015 mmol, 5% yield over 2 steps): ^1H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.8 (s, 1H), 8.1 (d, 1H), 7.8 (m, 2H), 7.6 (d, 1H), 7.2 (t, 1H); ES-MS (m/z) 269 $[M+1]^+$.

EXAMPLE 165

SYNTHESIS OF 5-{3-[4-(METHYLETHYL)PHENYL]-1H-INDAZOL-5-YL}-2H-1,2,3,4-TETRAZOLE



A. 3-[4-(Methylethyl)phenyl]-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound was prepared as described in Example 161, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.400 g, 1.30 mmol), in ethylene glycol dimethyl ether (10 mL), 4-isopropyl phenyl boronic acid (0.321 g, 1.96 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.150 g, 0.130 mmol), and potassium phosphate (1.38 g, 6.5 mmol): (0.364 g, 81 % yield): ES-MS (m/z) 346 $[M+1]^+$.

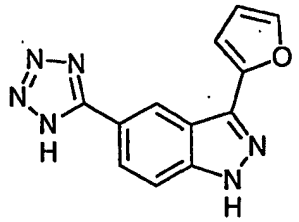
B. 5-{3-[4-(Methylethyl)phenyl]-1H-indazol-5-yl}-2H-1,2,3,4-tetrazole

The title compound was prepared from 3-[4-(methylethyl)phenyl]-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.095 g, 0.307 mmol), azidotributyl tin

(0.744 g, 0.689 mL, 2.33 mmol) in toluene (10 mL) as described for the preparation of compound 167. Deprotection was effected by treating a dioxane solution (5 mL) with 5 mL of 6.0 N aqueous solution of hydrogen chloride. The solid obtained upon completion of the reaction was partially dissolved in 2.0 N aqueous sodium hydroxide and was extracted in ethyl acetate (4 x 15 mL). (0.260 g, 0.85 mmol, 80% yield over 2 steps): ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 8.7 (s, 1H), 8.1 (d, 1H), 7.9 (d, 2H), 7.8 (d, 1H), 7.4 (d, 2H), 3.0 (septet, 1H), 1.3 (d, 6H); ES-MS (m/z) 305 $[M+1]^+$.

EXAMPLE 166

SYNTHESIS OF 2-(5-(2H-1,2,3,4-TETRAZOL-5-YL)-1H-INDAZOL-3-YL)FURAN



A. 3-(2-Furyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

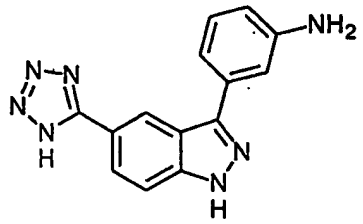
The title compound was prepared as described in Example 161, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.300 g, 0.98 mmol), in ethylene glycol dimethyl ether (10 mL), 2-furan boronic acid (0.164 g, 1.46 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.113 g, 0.098 mmol), and potassium phosphate (1.03 g, 4.9 mmol) (0.198 g, 69 % yield): ES-MS (m/z) 294 $[M+1]^+$.

B. 2-(5-(2H-1,2,3,4-Tetrazol-5-yl)-1H-indazole-3-yl)furan

The title compound was prepared from 3-(2-furyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.095 g, 0.307 mmol), azidotributyl tin (0.245 g, 0.202 mL, 0.74 mmol) in toluene (8 mL) as described for the preparation of compound 167. Deprotection was effected by treating a dioxane solution (5 mL) with 8 mL of 4.0N solution of hydrogen chloride in 1,4-dioxane. The compound was purified by preparative HPLC (10-100% acetonitrile in H_2O, 20 min) (0.008 g, 0.032 mmol, 4.7% yield over 2 steps): ^{1}H NMR (DMSO-d_6) δ 13.6 (br s, 1H), 8.8 (s, 1H), 8.1 (d, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.1 (d, 1H), 6.7 (dd, 1H); ES-MS (m/z) 253 $[M+1]^+$.

EXAMPLE 167

SYNTHESIS OF 3-(5-(2H-1,2,3,4-TETRAZOL-5-YL)-1H-INDAZOL-3-YL)PHENYLAMINE



A. 3-(3-Aminophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

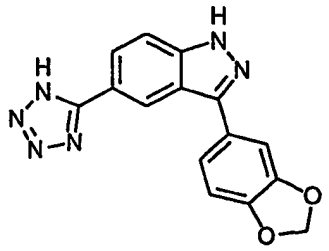
The title compound was prepared as described in Example 161, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.300 g, 0.98 mmol), in ethylene glycol dimethyl ether (10 mL), 3-aminophenyl boronic acid (0.227 g, 1.46 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.113 g, 0.098 mmol), and potassium phosphate (1.03 g, 4.9 mmol): (0.273 g, 87 % yield): ES-MS (m/z) 319 $[M+1]^+$.

B. 3-(5-(2H-1,2,3,4-Tetrazol-5-yl)-1H-indazole-3-yl)phenylamine

The title compound was prepared from 3-(3-aminophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.273 g, 0.86 mmol), azidotributyl tin (0.314 g, 0.260 mL, 0.95 mmol) in toluene (10 mL). The reaction mixture was heated to reflux temperature for 12 hours resulting in partial conversion to the desired product along with partially and fully deprotected final products. An additional amount of azidotributyl tin was added (0.260 mL) and the reaction was heated to reflux temperature for 18 hours. Toluene was removed under reduced pressure and the crude was dissolved in 5 mL of 1,4-dioxane, 5 mL of 6.0 N aqueous hydrogen chloride, and 2 mL of methanol. The reaction was then heated to 60°C for 2 days. The reaction was concentrated under reduced pressure and the pH was made basic by adding 2.0 N aqueous NaOH. The aqueous phase was washed with ethyl acetate (3 x 10 mL). The aqueous phase was then acidified using 6.0 N aqueous hydrogen chloride. The compound was filtered and purified by preparative HPLC (10-100% acetonitrile in H_2O, 20 min) (0.050 g, 0.18 mmol, 21% yield over 2 steps): ^1H NMR (DMSO-d_6) δ 13.8 (br s, 1H), 8.9 (s, 1H), 8.1 (d, 1H), 8.0 (d, 2H), 7.8 (d, 1H), 7.6 (t, 1H), 7.3 (d, 1H); ES-MS (m/z) 278 $[M+1]^+$.

EXAMPLE 168

SYNTHESIS OF 5-(5-(1H-1,2,3,4-TETRAAZOL-5-YL)-1H-INDAZOL-3-YL)-2H-BENZO[D]1,3-DIOXOLENE



A. 3-(2H-Benzo[d]1,3-dioxolen-5-yl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound (1.45 g, 63% yield) was prepared as described in Example 149 D using 3,4-(methylenedioxy)phenylboronic acid (1.64 g, 9.91 mmol). ES-MS (m/z) 348 $[M+1]^+$.

B. 3-(2H-benzo[d]1,3-dioxolen-5-yl)-1H-indazole-5-carbonitrile

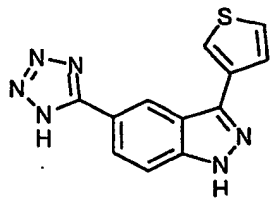
The title compound (790 mg, 78% yield) was prepared as described in Example 149 E using 3-(2H-benzo[d]1,3-dioxolen-5-yl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (1.33 g, 3.83 mmol). ES-MS (m/z) 264 $[M+1]^+$.

C. 5-(5-(1H-1,2,3,4-Tetraazol-5-yl)-1H-indazol-3-yl)-2H-benzo[d]1,3-dioxolene

The title compound (360 mg, 41% yield) was prepared as described in Example 170 A using 3-(2H-benzo[d]1,3-dioxolen-5-yl)-1H-indazole-5-carbonitrile (750 mg, 2.85 mmol). ^{1}H NMR (DMSO-d_6) δ 13.50 (s, 1H), 8.72 (s, 1H), 8.09 (d, 1H), 7.78 (d, 1H), 7.58-7.52 (m, 2H), 7.13 (d, 1H), 6.13 (s, 2H); ES-MS (m/z) 307 $[M+1]^+$.

EXAMPLE 169

SYNTHESIS OF 3-(5-(2H-1,2,3,4-TETRAZOL-5-YL)-1H-INDAZOL-3-YL)THIOPHENE



A. 1-Perhydro-2H-pyran-2-yl-3-(3-thienyl)-1H-indazole-5-carbonitrile

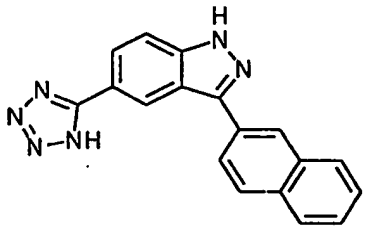
The title compound (0.233 g, 38 % yield) was prepared as described in Example 161, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.400 g, 1.30 mmol), in ethylene glycol dimethyl ether (10 mL), 3-thiophene boronic acid (0.251 g, 1.96 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.150 g, 0.130 mmol), and potassium phosphate (1.38 g, 6.5 mmol): ES-MS (m/z) 310 $[M+1]^+$.

B. 3-(5-(2H-1,2,3,4-Tetrazol-5-yl)-1H-indazol-3-yl)thiophene

The title compound was prepared from 1-perhydro-2H-pyran-2-yl-3-(3-thienyl)-1H-indazole-5-carbonitrile (0.233 g, 0.75 mmol), azidotributyl tin (0.375 g, 0.3 10 mL, 1.13 mmol) in toluene (10 mL) as described for the preparation of Example 167. Deprotection was effected by treating a dioxane solution (5 mL) with 5 mL of 6.0N aqueous solution of hydrogen chloride. The solid obtained upon completion of the reaction was partially dissolved in 3 mL of tetrahydrofuran and was precipitated out by adding 20 mL of hexanes (0.108 g, 0.85 mmol, 79% yield over 2 steps): ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 8.8 (s, 1H), 8.2 (t, 1H), 8.1 (dd, 1H), 7.8-7.7 (m, 3H); ES-MS (m/z) 269 $[M+1]^+$.

EXAMPLE 170

SYNTHESIS OF 5-(3-(2-NAPHTHYL)-1H-INDAZOL-5-YL)-1H-1,2,3,4-TETRAZOLE

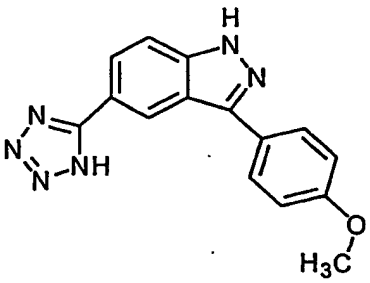


A. 5-(3-(2-naphthyl)-1H-indazol-5-yl)-1H-1,2,3,4-tetrazole

A mixture of 3-(2-naphthyl)-1H-indazole-5-carbonitrile (105 mg, 0.390 mmol), azidotributyltin (Bu_3SnN_3, 710 mg, 2.14 mmol, 5.49 equiv.), and 4.1 mL toluene was refluxed for 49.5 h and concentrated to an oil. The oil was stirred in 31 mL dioxane and 31 mL 6.0 N aq HCl at room temperature for 4 h. The mixture was partitioned between 6.0 N aq. NaOH and hexanes, and the layers separated. The aqueous layer was extracted with hexanes, and 2 x EtOAc, and then filtered. The aqueous layer was acidified to pH ca. 4.0 with 6.0 N aq. HCl. The resulting precipitate was either collected by filtration and dried in a vacuum oven, or extracted with EtOAc, dried (Na_2SO_4), filtered and concentrated to afford the title compound (78.4 mg, 64.3% yield): ^{1}H NMR (DMSO-d_6) δ 13.70 (s, 1H), 8.92 (s, 1H), 8.60 (s, 1H), 8.17 (d, 1H), 8.15-8.00 (m, 3H), 7.94 (d, 1H), 7.85 (d, 1H), 7.63-7.58 (m, 2H); ES-MS (m/z) 313 $[M+1]^+$.

EXAMPLE 171

SYNTHESIS OF 1-(5-(1H-1,2,3,4-TETRAAZOL-5-YL)(1H-INDAZOL-3-YL))-4-METHOXYBENZENE

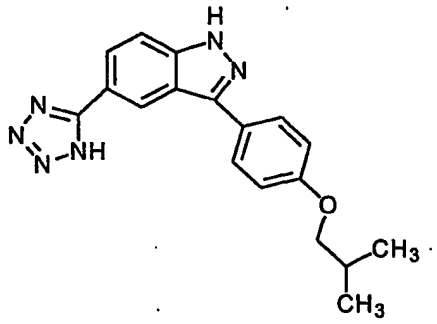


A. 1-(5-(1H-1,2,3,4-Tetraazol-5-yl)(1H-indazol-3-yl))-4-methoxybenzene

The title compound (92.6 mg 72.3% yield) was prepared as described in Example 170 A using 3-(4-methoxyphenyl)-1H-indazole-5-carbonitrile (109 mg, 0.437 mmol). ^{1}H NMR (DMSO-d_6) δ 13.42 (s, 1H), 8.73 (s, 1H), 8.10 (d, 1H), 7.98 (d, 2H), 7.73 (d, 1H), 7.18 (d, 2H), 3.85 (s, 3H); ES-MS (m/z) 293 $[M+1]^+$.

EXAMPLE 172

SYNTHESIS OF 1-(5-(1H-1,2,3;4-TETRAAZOL-5-YL)(1H-INDAZOL-3-YL))-4-(2-METHYLPROPOXY)BENZENE



A. 3-[4-(2-Methylpropoxy)phenyl]-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

A mixture of 3-(4-hydroxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (219 mg, 0.686 mmol), potassium carbonate (K_2CO_3, 568 mg, 4.12 mmol, 6.00 equiv.), 2.00 mL of dimethylformamide (DMF), and 1-bromo-2-methylpropane (Aldrich, 300 mg, 2.18 mmol, 3.20 equiv.) were stirred at room temperature for 2 h, and then heated at 40°C for 22 h. Additional potassium carbonate (568 mg, 4.12 mmol, 6.00 equiv.), and 1-bromo-2-methylpropane (Aldrich, 300 mg, 2.18 mmol, 3.20 equiv.) were added, and heating continued for another 28 h. The mixture was diluted with EtOAc, washed with 2 x sat. aq. $NaHCO_3$, 2 x sat. aq. NaCl, and dried (Na_2SO_4). Purification by silica gel chromatography using 20% EtOAc in hexanes afforded the title compound (190 mg, 73.6% yield): ES-MS (m/z) 376 $[M+1]^+$.

B. 3-[4-(2-Methylpropoxy)phenyl]-1H-indazole-5-carbonitrile

The title compound was prepared as described in Example 149 E using 3-[4-(2-methylpropoxy)phenyl]-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (186 mg,

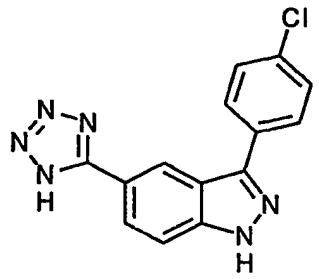
0.495 mmol) to provide the title compound (83.7 mg, 58.1% yield): ES-MS (m/z) 292 $[M+1]^+$.

C. 1-(5-(1H-1,2,3,4-Tetraazol-5-yl)(1H-indazole-3-yl))-4-(2-methylpropoxy)benzene

The title compound was prepared as described in Example 170.A using 3-[4-5 (2-methylpropoxy)phenyl]-1H-indazole-5-carbonitrile (83.7 mg, 0.287 mmol) to provide the title compound (58.2 mg, 60.6% yield): ^{1}H NMR (DMSO-d_6) δ 13.47 (s, 1H), 8.78 (s, 1H), 8.14 (d, 1H), 7.99 (d, 2H), 7.78 (d, 1H), 7.16 (d, 2H), 3.82 (d, 2H), 2.06 (m, 1H), 1.02 (d, 6H); ES-MS (m/z) 33S $[M+1]^+$.

EXAMPLE 173

SYNTHESIS OF 5-[3-(4-CHLOROPHENYL)-1H-INDAZOL-5-YL]-2H-1,2,3,4-TETRAZOLE



A. 3-(4-Chlorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound was prepared as described in Example 161, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.400 g, 1.30 mmol), in ethylene glycol dimethyl ether (10 mL), 4-chlorophenyl boronic acid (0.306 g, 1.96 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.150 g, 0.130 mmol), and potassium phosphate (1.38g, 6.5 mmol): (0.351 g, 80 % yield): ES-MS (m/z) 338 $[M+1]^+$.

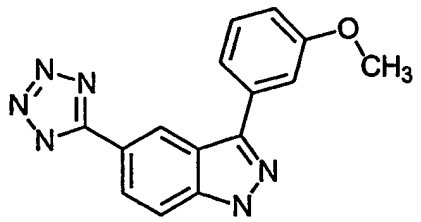
B. 5-[3-(4-Chlorophenyl)-1H-indazol-5-yl]-2H-1,2,3,4-tetrazole

The title compound was prepared from 3-(4-chlorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.35 1 g, 1.04 mmol), azidotributyl tin (0.351 g, 0.627 mL, 2.29 mmol) in toluene (10 mL) as described for the preparation of compound 167. Deprotection was effected by treating a dioxane solution (5 mL) with 5 mL of 6.0N

aqueous solution of hydrogen chloride. Half of the solid obtained upon completion of the reaction was purified by preparatory HPLC (0.054 g, 0.18 mmol, 35% yield over 2 steps) ^{1}H NMR (DMSO-d_6) 13.7 (s, 1H), 8.8 (s, 1H), 8.1 (t, 3H), 7.8 (d, 1H), 7.6 (t, 2H); ES-MS (m/z) 297 $[M+1]^+$.

EXAMPLE 174

SYNTHESIS OF 1-(5-(2H-1,2,3,4-TETRAZOL-5-YL)(1H-INDAZOL-3-YL))-3-METHOXYBENZENE



A. 3-(3-Methoxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound was prepared as described in Example 161, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.350 g, 1.14 mmol), in ethylene glycol dimethyl ether (10 mL), 3-methoxy phenyl boronic acid (0.260 g, 1.71 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.131 g, 0.114 mmol), and potassium phosphate (1.20 g, 5.7 mmol): (0.333 g, 87 % yield): ES-MS (m/z) 334 $[M+1]^+$.

B. 1-(5-(2H-1,2,3,4-Tetrazol-5-yl)(1H-indazol-3-yl))-3-methoxybenzene

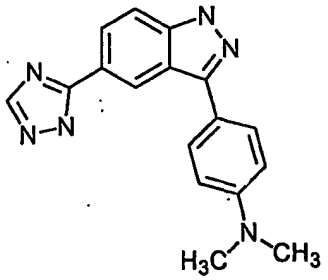
The title compound was prepared from 3-(3-methoxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.333 g, 1.00 mmol), azidotributyl tin (0.664 g, 0.548 mL, 2.0 mmol) in toluene (10 mL) as described for the preparation of Example 167. Deprotection was effected by treating a dioxane solution (5 mL) with 5 mL of 6.0 N aqueous solution of hydrogen chloride. The solvent was removed under reduced pressure and the crude was extracted into 10 mL of 2.0 N aqueous sodium hydroxide solution. Impurities were washed with ethyl acetate (3x10 mL). The product was collected by filtration after addition of 6.0 N HCl and was washed with small portions of water (0.092 g, 0.18 mmol, 31.5% yield over 2 steps): ^{1}H NMR (DMSO-d_6) δ 13.6 (br s, 1H), 8.8 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.48-7.55 (m, 3H), 7.0 (dd, 1H), 3.9 (s, 3H); ES-MS (m/z) 293 $[M+1]^+$.

A. 4-(5-(1H-1,2,4-triazol-5-yl)-1H-indazol-3-yl)phenol

A mixture of 3-(4-hydroxyphenyl)-1H-indazole-5-carboxamide (100 mg, 0.425 mmol) and N,N-dimethylformamide dimethyl acetal (10.0 mL, 75.3 mmol, 177 equiv.) was heated at 90°C for 3 h. The reaction mixture was separated from some dark residue via pipet and concentrated. To the concentrate was added 20 mL of glacial acetic acid (AcOH), and anhydrous hydrazine (357 mg, 11.1 mmol, 26.1 equiv.). The mixture was heated at 90°C for 2 h. Water (50 mL) was added to the mixture, and the acetic acid was removed on a rotary evaporator. The remaining mixture was extracted with EtOAc. The combined organics were dried (Na_2SO_4) and purified by prep HPLC to afford the title compound (11.4 mg, 9.7% yield): ^{1}H NMR (DMSO-d_6) δ 13.25 (br s, 1H), 9.70 (br, 2H), 8.64 (s, 1H), 8.42 (br s, 1H) 8.05 (d, 1H), 7.83 (d, 2H), 7.65 (d, 1H), 6.95 (d, 2H); ES-MS (m/z) 278 $[M+1]^+$.

EXAMPLE 183

SYNTHESIS OF [4-(5-(1H-1,2,4-TRIAZOL-5-YL)(1H-INDAZOL-3-YL))PHENYL]DIMETHYLAMINE

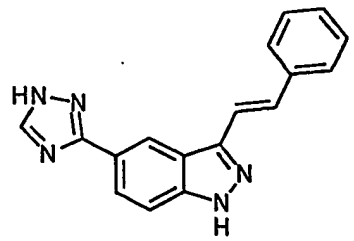


A. [4-(5-(1H-1,2,4-Triazol-5-yl)(1H-indazole-3-yl))phenyl]dimethylamine

A mixture of 3-[4-(dimethylamino)phenyl]-1H-indazole-5-carboxamide (60 mg, 0.214 mmol) and N,N-dimethylformamide dimethyl acetal (10.0 mL, 75.3 mmol, 352 equiv.) was heated at 93°C for 4.5 h and then concentrated. To the concentrate was added 4.0 mL of glacial acetic acid (AcOH), and anhydrous hydrazine (180 mg, 5.62 mmol, 26.3 equiv.). The mixture was heated at 93°C for 3 h and concentrated. The residue was partitioned between EtOAc and 6.0 N aq. NaOH and the layers separated. The aqueous layer was extracted with 2 x EtOAc and then the pH adjusted between 10-11 with 6.0 N aq. HCl. The resulting precipitate was collected by filtration, washed with H_2O, and dried in a vacuum oven to afford the title compound (191 mg, 29.3% yield): ^{1}H NMR (DMSO-d_6 D_2O containing one drop of aqueous HCl) δ 9.30 (s, 1H), 8.89 (s, 1H), 8.27 (d, 2H), 8.12 (d, 1H), 7.96-7.88 (m, 3H), 3.29 (s, 6H); ES-MS (m/z) 305 $[M+1]^+$.

EXAMPLE 184

SYNTHESIS OF 3-[3-((1E)-2-PHENYLVINYL)-1H-INDAZOL-5-YL]-1H-1,2,4-TRIAZOLE



A. 3-((1E)-2-Phenylvinyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

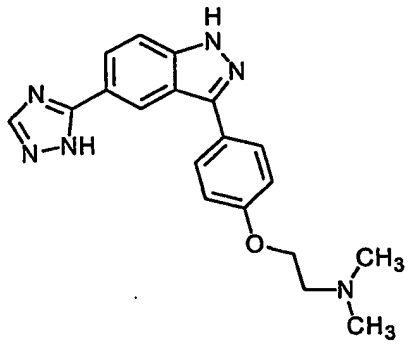
The synthesis of the title compound was performed as described in Example 180.

B. 3-[3-((1E)-2-Phenylvinyl)-1H-indazol-5-yl]-1H-1,2,4-triazole

Compound 3-((1E)-2-phenylvinyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.126 g, 0.38 mmol) was suspended in 2.50 mL of ethanol and 0.10 mL of water. To this suspension, hydrogen peroxide (30% commercial solution, 3.40 mL), and aqueous sodium hydroxide (6.0 N, 0.320 mL) were added. The reaction mixture was heated to 45°C for 14 hours. Acidification of the reaction mixture with aqueous hydrogen chloride (6.0 N) to pH 5 resulted in the formation of a white precipitate that was filtered and washed with small portions of water. The product was dried under vacuum. The solid was dissolved in N,N-dimethyl formamide dimethyl acetal (20 mL) and heated to reflux temperature for 2 hours. The white solid formed upon addition of 5 mL of water, was collected, washed with water and dried overnight in a vacuum oven. The solid was dissolved in 20 mL of acetic acid and 1.5 mL of anhydrous hydrazine was added. The solution was heated to 80°C for 12 hours resulting in the formation of the triazole substituent as well as deprotection of the indazole nitrogen. Solvents were removed under reduced pressure and the title compound was isolated after purification by preparative HPLC (0.040 g, 36% yield over 4 steps): ^{1}H NMR (DMSO-d_6) δ 8.8 (s, 1H), 8.5 (s, 1H), 8.0 (dd, 1H), 7.7 (d, 2H), 7.6 (d, 1H), 7.55 (d, 1H), 7.5 (d, 1H), 7.4 (t, 1H), 7.3 (t, 1H); ES-MS (m/z) 288 $[M+1]^+$.

EXAMPLE 185

SYNTHESIS OF {2-[4-(5-(1H-1,2,4-TRIAZOL-5-YL)(1H-INDAZOL-3-YL))PHENOXY]ETHYL}DIMETHYLAMINE

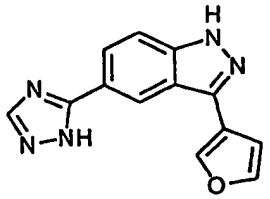


A. {2-[4-(5-(1H-1,2,4-Triazol-5-yl)(1H-indazol-3-yl))phenoxy]ethyl}dimethylamine

A mixture of 3-{4-[2-(dimethylamino)ethoxy]phenyl}-1H-indazole-5-carboxamide (79 mg, 0.243mmol) and N,N-dimethylformamide dimethyl acetal (10.0 mL, 75.3 mmol, 310 equiv.) was heated at 93 °C for 3 h and then concentrated. To the concentrate was added 4.0 mL of glacial acetic acid (AcOH), and anhydrous hydrazine (204 mg, 6.36 mmol, 26.2 equiv.). The mixture was heated at 93 °C for 3 h and concentrated. The residue was partitioned between EtOAc and 6.0 N aq. NaOH and the layers separated. The aqueous layer was extracted with 2 x EtOAc and then the pH adjusted between 10-11 with 6.0 N aq. HCl to give maximum cloudiness. The mixture was extracted with 3 x EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated to afford the title compound (73.3 mg, 86.5% yield): ^{1}H NMR (DMSO-d_6) δ 14.20 (br s, 1H), 13.30 (br s, 1H), 8.65 (s, 1H), 8.37 (br s, 1H), 8.07 (d, 1H), 7.96 (d, 2H), 7.65 (d, 1H), 7.15 (d, 2H), 4.14 (t, 2H), 2.67 (t, 2H), 2.24 (s, 6H); ES-MS (m/z) 349 $[M+1]^+$.

EXAMPLE 186

SYNTHESIS OF 3-(5-(1H-1,2,4-TRIAZOL-5-YL)-1H-INDAZOL-3-YL)FURAN

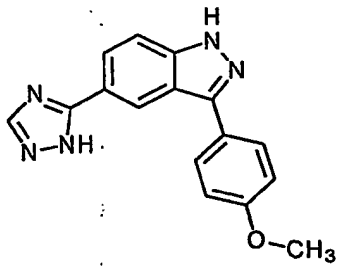


A. 3-(5-(1H-1,2,4-Triazol-5-yl)-1H-indazol-3-yl)furan

The title compound was prepared as described in Example 184 B to provide the title compound (60 mg, 55% yield). ^{1}H NMR (DMSO-d_6) δ 14.2 (m, 1H), 13.3 (br s, 1H), 8.59 (br s, 1H), 8.45 (br s, 1H), 8.10 (br s, 1H), 8.07 (br s, 1H), 7.88 (s, 1H), 7.67 (m, 1H), 7.06 (br s, 1H); ES-MS (m/z) 252 $[M+1]^+$.

EXAMPLE 187

SYNTHESIS OF 1-(5-(1H-1,2,4-TRIAZOL-5-YL)(1H-INDAZOL-3-YL))-4-METHOXYBENZENE

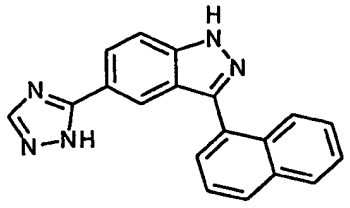


A. 1-(5-(1H-1,2,4-triazol-5-yl)(1H-indazol-3-yl))-4-methoxybenzene

The title compound was prepared as described in Example 185 A using 3-(4-methoxyphenyl)-1H-indazole-5-carboxamide (200 mg, 0.748 mmol) to provide the title compound (166 mg, 76.1% yield): ^{1}H NMR (DMSO-d_6) δ 13.6 (br s, 1H), 8.73 (s, 1H), 8.22 (s, 1H), 8.05 (d, 1H), 7.95 (d, 2H), 7.63 (d, 1H), 7.13 (d, 2H), 3.84 (s, 3H); ES-MS (m/z) 292 $[M+1]^+$.

EXAMPLE 188

SYNTHESIS OF 5-(3-NAPHTHYL-1H-INDAZOL-5-YL)-1H-1,2,4-TRIAZOLE



A. 3-Naphthyl-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound (298 mg, 64.4% yield) was prepared as described in Example 149 D using 1-naphthylboronic acid (336 mg, 1.95 mmol). ES-MS (m/z) 354 $[M+1]^+$.

B. 3-Naphthyl-1H-indazole-5-carbonitrile

The title compound (108 mg, 47.6% yield) was prepared as described in Example 149 E using 3-naphthyl-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (298 mg, 0.843 mmol). ES-MS (m/z) 270 $[M+1]^+$.

C. 3-Naphthyl-1H-indazole-5-carboxamide

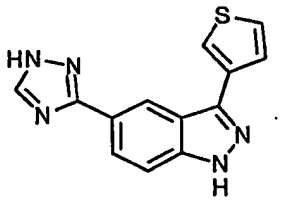
The title compound (71.4 mg, 62.1% yield) was prepared as described in Example 149 F using 3-naphthyl-1H-indazole-5-carbonitrile (108 mg, 0.401 mmol). ES-MS (m/z) 288 $[M+1]^+$.

D. 5-(3-Naphthyl-1H-indazole-5-yl)-1H-1,2,4-triazole

The title compound was prepared as described in Example 185 A using 3-naphthyl-1H-indazole-5-carboxamide (71.4 mg, 0.248 mmol). Further purification by prep HPLC afforded the title compound (26.8 mg, 34.7% yield): ^{1}H NMR (DMSO-d_6) δ 13.58 (br s, 1H), 8.38 (br s, 1H), 8.27-8.22 (m, 2H), 8.17-8.03 (m, 3H), 7.83-7.67 (m, 3H), 7.62-7.52 (m, 2H); ES-MS (m/z) 312 $[M+1]^+$.

EXAMPLE 189

SYNTHESIS OF 3-(5-(1H-1,2,4-TRIAZOL-3-YL)-1H-INDAZOL-3-YL)THIOPHENE



A. 1-Perhydro-2H-pyran-2-yl-3-(3-thienyl)-1H-indazole-5-carbonitrile

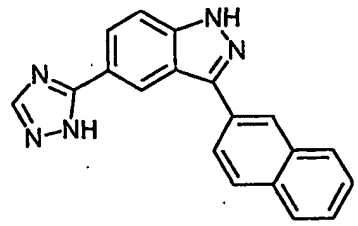
The title compound was prepared according to the procedure described for compound 184, using 3-bromo-1-perhydro-2H-pyran-2- yl-1H-indazole-5-carbonitrile (0.300 g, 0.98 mmol), in ethylene glycol dimethyl ether (10 mL), 3-thiophene boronic acid (0.450 g, 1.47 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.113 g, 0.098 mmol), and potassium phosphate (1.04 g, 4.9 mmol) (0.159 g, 52 % yield): ES-MS (m/z) 310 $[M+H]^+$.

B. 3-(5-(1H-1,2,4-Triazol-3-yl)-1H-indazol-3-yl)thiophene

Hydrolysis of 1-perhydro-2H-pyran-2-yl-3-(3-thienyl)-1H-indazole-5-carbonitrile (0.159 g, 0.51 mmol) 1-perhydro-2H-pyran-2-yl-3-(3-thienyl)-1H-indazole-5-carboxamide using hydrogen peroxide (30% commercial solution, 5.00 mL) and aqueous sodium hydroxide (6.0 N, 0.400 mL) did not result in satisfactory conversion after 18 hours at 45°C. So the reaction mixture was submitted to THP hydrolysis conditions (4.0N HCl in dioxane, 5 mL, and 6.0 N aqueous HCl, 5 mL; 60°C, 4 hours) before performing the conversion of the nitrile intermediate to the primary amide (4 mL of 30% hydrogen peroxide, 0.2 mL of 6.0 N aqueous sodium hydroxide, 50°C, 2 hours). Precipitation of the intermediate was induced by addition of water. 3-(3-thienyl)-1H-indazole-5-carboxamide was converted to (2E)-2-aza-3-(dimethylamino)-1-(3-(3-Thienyl)(1H-indazol-5-yl))prop-2-en-1-one upon heating a N,N-dimethyl formamide dimethyl acetal (10 mL) to reflux temperature. Cyclization to the final compound was achieved by treating an acetic acid solution of amidine intermediate (10 mL) with 1.0 mL of anhydrous hydrazine at reflux temperature for 2 hours. After aqueous work-up, the title compound was purified by preparative HPLC (15-80% acetonitrile in water) (0.012 g, 9% yield over 4 steps): ^{1}H NMR (DMSO-d_6) δ 13.3 (br s, 1H), 8.7 (s, 1H), 8.4 (br s, 1H), 7.75-8.1 (m, 2H), 7.7-7.6 (m, 4H); ES-MS (m/z) 268 $[M+H]^+$.

EXAMPLE 190

SYNTHESIS OF 5-(3-(2-NAPHTHYL)-1H-INDAZOL-5-YL)-1H-1,2,4-TRIAZOLE

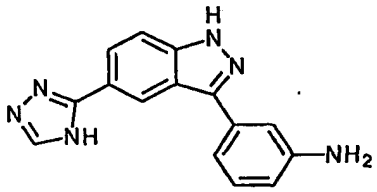


A. 5-(3-(2-Naphthyl)-1H-indazol-5-yl)-1H-1,2,4-triazole

The title compound (79.3 mg, 55.4% yield) was prepared as described in Example 185 A using 3-(2-naphthyl)-1H-indazole-5-carboxamide (132 mg, 0.459 mmol). ^{1}H NMR (DMSO-d_6) δ 13.4-13.2 (m, 1H), 11.99 (s, 0.42H, partial NH), 9.67-8.50 (m, 3H), 8.22-7.97 (m, 5H), 7.79-7.67 (m, 1H), 7.64-7.55 (m, 2H); ES-MS (m/z) 312 $[M+1]^+$.

EXAMPLE 191

SYNTHESIS OF 3-(5-(1H-1,2,4-TRIAZOL-3-YL)-1H-INDAZOL-3-YL) PHENYLAMINE



A. 3-(3-Aminophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound (0.420 g, 81 % yield) was prepared according to the procedure described for compound 184, using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.500 g, 1.63 mmol), in ethylene glycol dimethyl ether (10 mL), 3-aminophenyl boronic acid (0.380 g, 2.45 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.188 g, 0.16 mmol), and potassium phosphate (1.72 g, 8.15 mmol): ES-MS (m/z) 319 $[M+H]^+$.

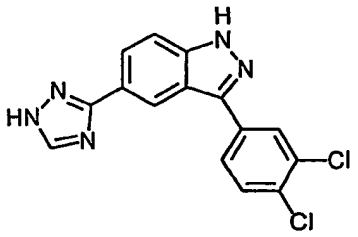
B. 3-(5-(1H-1,2,4-Triazol-3-yl)-1H-indazol-3-yl)phenylamine

The tetrahydropyran protecting group was removed under acidic conditions

using 5 mL of 4.0 N HCl solution in dioxane, and 2.5 mL of aqueous HCl at 60°C for 2 hours added to 3-(3-aminophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.220g, 0.69 mmol). The reaction mixture was neutralized with 2.0 N aqueous sodium hydroxide and extracted with ethyl acetate. After evaporation of the solvent, the residue was dissolved in 4.0 mL of absolute ethanol and reacted with 4.0 mL of 30% commercial hydrogen peroxide solution and 0.2 mL of 6.0 N aqueous sodium hydroxide solution. The reaction mixture was heated to 45°C for 2 hours. After neutralization and extraction in ethyl acetate, the intermediate was dissolved in 10 mL of dimethoxydimethyl formamide acetal and heated to reflux temperature of the solvent for 2 hours. After evaporation of the solvent, the final cyclization was performed by treating a solution of the precursor in acetic acid (5 mL), with 1 mL of anhydrous hydrazine at 80°C for 2 hours. The title compound was purified by preparative HPLC (0.011 g, 5% yield over 4 steps): ^{1}H NMR (DMSO-d_6) 13.4 (br s, 1H), 10.1 (s, 1H), 8.7 (s, 1H), 8.2 (s, 1H), 8.1 (d, 1H), 7.7 (t, 3H), 7.5 (t, 1H); ES-MS (m/z) 319 $[M+H]^+$.

EXAMPLE 192

SYNTHESIS OF 3-[3-(3,4-DICHLOROPHENYL)-1H-INDAZOL-5-YL]-1H-1,2,4-TRIAZOLE



A. 3-(3,4-dichlorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound was prepared according to the procedure described in Example 184 using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.300 g, 0.98 mmol), in ethylene glycol dimethyl ether (10 mL), 3,4-dichlorophenyl boronic acid (0.279 g, 1.46 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.13 g, 0.098 mmol), and potassium phosphate (1.03 g, 4.9 mmol) (0.249 g, 74 % yield): ES-MS (m/z) 372 $[M+1]^+$.

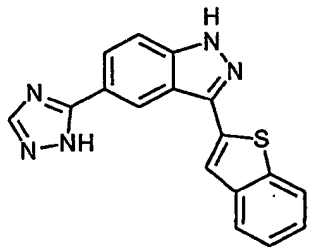
B. 3-[3-(3 ,4-Dichlorophenyl)-1H-indazol-5-yl]-1H-1,2,4-triazole

The tetrahydropyran protecting group was removed under acidic conditions

using 4 mL of 4.0 N HCl solution in dioxane, and 4 mL of aqueous HCl (6.0 N) at 60°C for 2 hours added to 3-(3,4-dichlorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (0.220 g, 0.69 mmol). The residue was dissolved in 4.0 mL of absolute ethanol and reacted with 4.0 mL of 30 % commercial hydrogen peroxide solution and 0.3 mL of 6.0 N aqueous sodium hydroxide solution. The reaction mixture was heated to 80°C for 1 hour. The intermediate was dissolved in 8 mL of dimethoxydimethyl formamide acetal and heated to reflux temperature of the solvent for 1 hour. Cyclization to the final compound was achieved by treating an acetic acid solution of the amidine intermediate (10 mL) in the presence of 1.0 mL of anhydrous hydrazine. The title compound was purified by preparative HPLC (0.030 g, 13% yield over 4 steps): ^{1}H NMR (DMSO-d_6) δ 8.7 (s, 1H), 8.4 (br s, 1H), 8.2 (d, 1H), 8.1 (d, 1H), 8.05 (d, 1H), 7.8 (d, 1H), 7.7 (d, 1H); ES-MS (m/z) 331 $[M+1]^+$.

EXAMPLE 193

SYNTHESIS OF 3-(5-(1H-1,2,4-TRIAZOL-5-YL)-1H-INDAZOL-3-YL)BENZO[B]THIOPHENE

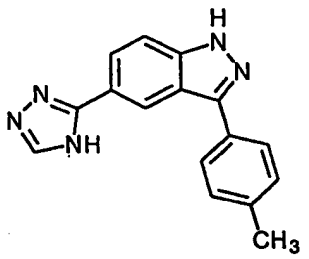


A. 3-(5-(1H-1,2,4-triazol-5-yl)-1H-indazol-3-yl)benzo[b]thiophene

The title compound was prepared as described in Example 185 A using 3-benzo[b]thiophen-3-yl-1H-indazole-5-carboxamide (112 mg, 0.382 mmol). Further purification by prep HPLC afforded the title compound (32.3 mg, 26.7% yield): ^{1}H NMR (DMSO-d_6) δ 13.60 (s, 1H), 8.85 (s, 1H), 8.45 (br, 1H), 8.18-8.11 (m, 2H), 8.07-7.98 (m, 2H), 7.75 (d, 1H), 7.50-7.48 (m, 2H); ES-MS (m/z) 318 $[M+1]^+$.

EXAMPLE 194

SYNTHESIS OF 3-[3-(4-METHYLPHENYL)-1H-INDAZOL-5-YL]-1H-1,2,4-TRIAZOLE



A. 3-Bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carboxamide

To a solution of 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (2.6 g, 8.48 mmol) in 20 mL of ethanol was added 20 mL of commercial solution of hydrogen peroxide (30%) and 1.8 mL of aqueous solution of sodium hydroxide (6.0 N). The suspension was heated to 50°C for 20 min. The reaction mixture was cooled down and neutralized with 6.0 N aqueous HCl. Further precipitation was observed upon addition of water (20 mL). The solid was collected by filtration, washed with small portions of water and dried in a vacuum oven at 40°C (2.6 g, 95% yield) ^{1}H NMR ($CDCl_3$) δ 8.2 (s, 1H), 8.0 (d, 1H), 7.7 (br s, 1H), 7.6 (d, 1H), 6.4 (br s, 1H), 5.7 (dd, 1H), 4.0 (m, 1H), 3.75 (m, 1H), 2.5 (m, 1H), 2.0 (m, 2H), 1.7 (m, 3H); ES-MS (m/z) 276 $[M+H]^+$.

B. (2E)-2-aza-3-(dimethylamino)-1-(3-bromo-1-perhydro-2H-pyran-2-yl-(1H-indazol-5-yl))prop-2-en-1-one

3-Bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carboxamide (2.6 g, 8.04 mmol) and the resulting solution was heated to 80°C for 2 hours. The solvent was removed under reduced pressure to afford the title compound that was used without further purification: ES-MS (m/z) 379 $[M+1]^+$.

C. 2-(5-(1H-1,2,4-triazol-3-yl)-3-bromo-1H-indazoyl)perhydro-2H-pyran

To a solution of (2E)-2-aza-3-(dimethylamino)-1-(3-bromo-1-perhydro-2H-pyran-2-yl(1H-indazol-5-yl))prop-2-en-1-one in 25 mL of acetic acid was added 3 mL of anhydrous hydrazine. The solution was heated to 80°C for 0.5 hour during which the formation of a precipitate and discoloration were observed. Complete precipitation of the product was achieved upon addition of 50 mL of water. The title compound was collected

by filtration, washed with small portions of water, and dried in a vacuum oven (40°C) (2.78 g, quantitative yield): ^{1}H NMR ($CDCl_3$) δ 8.3 (d, 1H), 8.1 (d, 1H), 7.6 (d, 1H), 5.7 (d, 1H), 4.0 (m, 1H), 3.75 (m, 1H), 2.5 (m, 1H), 2.0 (m, 2H), 1.7 (m, 3H); ES-MS (m/z) 348 $[M+1]^+$.

D. 2-{3-Bromo-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran

To a solution of 2-(5-(1H-1,2,4-triazol-3-yl)-3-bromo-1H-indazoyl)perhydro-2H-pyran in 60 mL in dimethyl formamide, was added triphenylmethyl chloride (3.48 g, 12.5 mmol), and triethyl amine (4.64 mL, 33.32 mmol). The reaction mixture was heated to 80°C for 12 hours. The solvent was removed under reduced pressure and the crude reaction mixture was partitioned between water and ethyl acetate. The oil resulting from evaporation of the extracts was purified by column chromatography (SiO_2, 25 % ethyl acetate in hexanes (2.90 g, 61% over 4 steps): ^{1}H NMR ($CDCl_3$) δ 8.3 (s, 1H), 8.2 (d, 1H), 7.9 (s, 1H), 7.5 (d, 1H), 7.4-8.1 (m, 15H), 5.68 (dd, 1H), 4.0 (m, 1H), 3.75 (m, 1H), 2.5 (m, 1H), 2.1 (m, 2H), 1.7 (m, 3H); ES-MS (m/z) 592 $[M+2]^+$.

E. 2-{3-(4-Methylphenyl)-5-[1-(trimethylphenyl)(1,2,4-triazol-3-yl)]-1H-indazoyl}perhydro-2H-pyran

To a solution of 2-{3-bromo-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran (0.150 g, 0.254 mmol), in ethylene glycol dimethyl ether (3 mL) was added 4-methylphenyl boronic acid (0.052 g, 0.381 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.030 g, 0.0254 mmol) and potassium phosphate (0.269 g, 1.27 mmol). The reaction mixture was heated to reflux temperature for 5 hours. The solvent was then evaporated to dryness and the residue was dissolved in 20 mL of ethyl acetate. The heterogeneous solution was washed 3 times with 10 mL of water and once with 10 mL of brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The resulting brown solid was adsorbed on silica gel and purified by column chromatography (85:15 hexanes/ethyl acetate) to provide the title compound (0.130 g, 85 % yield): ES-MS (m/z) 602 $[M+1]^+$.

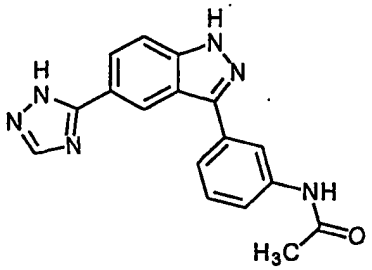
F. 3-[3-(4-Methylphenyl)-1H-indazol-5-yl]-1H-1,2,4-triazole

2-{3-(4-Methylphenyl)-5-[1-(trimethylphenyl)(1,2,4-triazol-3-yl)]-1H-indazoyl}perhydro-2H-pyran (0.130 g, 0.216 mmol) was dissolved in 4 mL of 4.0 N HCl in dioxane and 2 mL of 6.0 N aqueous HCl were added. After 2 hours at room temperature,

the reaction mixture was neutralized using aqueous sodium hydroxide (6.0 N) and the product was extracted with ethyl acetate. The extracts were dried under vacuum and dissolved in 5 mL of 6.0 N aqueous sodium hydroxide, side products extracted twice with diethyl ether. The aqueous phase was neutralized with 6.0 N HCl and the product was extracted with ethyl acetate. The crude was purified by preparative HPLC (15-80% acetonitrile in water) (0.024 g, 40% yield): ^{1}H NMR (DMSO-d_6) δ 13.4 (br s, 1H), 8.7 (s, 1H), 8.4 (br s, 1H), 8.1 (dd, 1H), 7.9 (d, 2H), 7.7 (d, 1H), 7.4 (d, 2H), 7.0 (d, 1H), 2.4 (s, 3H); ES-MS (m/z) 276 $[M+1]^+$.

EXAMPLE 195

SYNTHESIS OF N-[3-(5-(1H-1,2,4-TRIAZOL-3-YL)-1H-INDAZOL-3-YL)PHENYL]ACETAMIDE

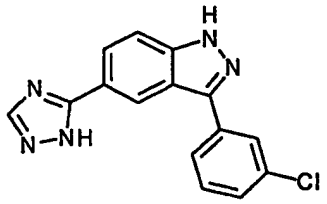


To a solution 3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazole-3-yl}phenylamine (0.200 g, 0.63 mmol), in acetic acid (6.0 mL) was added acetic anhydride (0.178 mL, 1.89 mmol). The reaction mixture was heated to reflux temperature for 12 hours. Water was added (10 mL) and the mixture was neutralized with 2.0 N aqueous sodium hydroxide. The product was extracted with ethyl acetate and concentrated to dryness. The crude oil was dissolved in 4 mL of ethanol and treated with 4 mL of commercial solution of hydrogen peroxide and 0.200 mL of 2.0 N aqueous sodium hydroxide. After 3 hours, the solvent was removed under reduced pressure. The resulting oil was dissolved in 5 mL of dimethoxy dimethyl formamide acetal and the solution was heated to reflux temperature for 3 hours. The solvent was removed under reduced pressure and the residue was dissolved in 10 mL of acetic acid and treated with 1 mL of anhydrous hydrazine. The reaction mixture was heated to reflux temperature for 12 hours. After neutralization with aqueous sodium hydroxide (2.0 N), the crude was extracted with ethyl acetate and purified by preparative HPLC (15-80% acetonitrile in water) (0.040 g, 20% over 5 steps): ^{1}H NMR (DMSO-d_6) δ 13.4 (br s, 1H), 10.1 (s, 1H), 8.7 (s, 1H), 8.4 (br s, 1H), 8.2 (s, 1H),

8.1 (d, 1H), 7.7 (t, 3H), 7.5 (t, 1H), 2.1 (s, 3H); ES-MS (m/z) 319 $[M+1]^+$.

EXAMPLE 196

SYNTHESIS OF 5-[3-(3-CHLOROPHENYL)-1H-INDAZOL-5-YL]-1H-1,2,4-TRIAZOLE

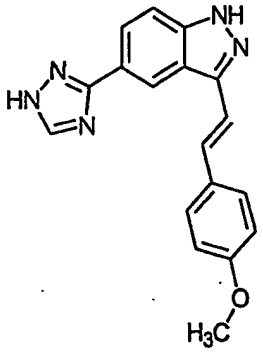


A. 5-[3-(3-Chlorophenyl)-1H-indazol-5-yl]-1H-1,2,4-triazole

The title compound was prepared as described in Example 189 B (55% yield). ^{1}H NMR (DMSO-d_6) δ 13.7 (br s, 1H), 8.74 (s, 1H), 8.53 (br s, 1H), 8.13 (d, 1H), 8.04-8.01 (m, 2H), 7.75 (d, 1H), 7.64 (t, 1H), 7.53 (d, 1H); ES-MS (m/z) 296 $[M+1]^+$.

EXAMPLE 197

SYNTHESIS OF 1-[(1E)-2-(5-(1H-1,2,4-TRIAZOL-3-YL)((1H-INDAZOL-3-YL))VINYL]-4-METHOXYBENZENE



A. 1-((1 E)-2-{1-Perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazole-3-yl)}vinyl-4-methoxybenzene

The title compound was prepared according to the procedure described in Example 194 using 2-{3-bromo-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran (0.150 g, 0.254 mmol), in ethylene glycol dimethyl ether

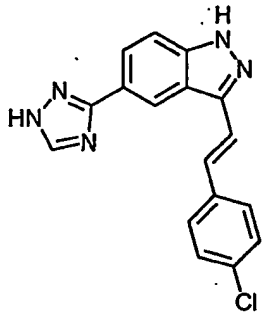
(3 mL), trans-4-methoxyphenylethenyl boronic acid (0.067 g, 0.375 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.030 g, 0.0254 mmol), and potassium phosphate (0.269 g, 1.27 mmol) (0.105 g, 64% yield): ES-MS (m/z) 644 $[M+H]^+$.

B. 1-[(1E)-2-(5-(1H-1,2,4-Triazol-3-yl)((1H-indazol-3-yl))vinyll-4-methoxybenzene

Hydrolysis was performed by stirring 1-((1E)-2-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}vinyl-4-methoxybenzene in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl at room temperature for 6.5 hours. A mixture of 2 isomers was isolated after purification by preparative HPLC (3% of the minor isomer) (0.014 g, 17.4% yield) ^1H NMR (DMSO-d_6) δ 8.8 (s, 1H), 8.55 (s, 1H), 8.15 (d, 1H), 7.7 (t, 3H), 7.5 (d, 2H), 7.0 (d, 2H), 3.8 (s, 3H); ES-MS (m/z) 318 $[M+1]^+$.

EXAMPLE 198

SYNTHESIS OF 3-{3-[(1E)-2-(4-CHLOROPHENYL)VINYL]-1H-INDAZOL-5-YL}-1H-1,2,4-TRIAZOLE



A. 2-{3-[(1 E)-2-(4-Chlorophenyl)vinyl]-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazoyl}perhydro-2H-pyran

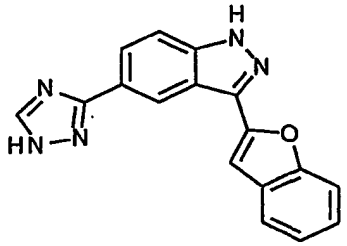
The title compound was prepared according to the procedure described in Example 194 using 2-{3-bromo-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran (0.160 g, 0.27 1 mmol), in ethylene glycol dimethyl ether (3 mL), trans-4-chlorophenylethenyl boronic acid (0.074 g, 0.406 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.031 g, 0.027 mmol), and potassium phosphate (0.287 g, 1.35 mmol) (0.146 g, 83% yield): ES-MS (m/z) 648 $[M+1]^+$.

B. 3-{3-[(1E)-2-(4-Chlorophenyl)vinyl]-1H-indazol-5-yl}-1H-1,2,4-triazole

Hydrolysis was performed by stirring 2-{3-[(1E)-2-(4-chlorophenyl)vinyl]-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazoyl}perhydro-2H-pyran in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl, at room temperature for 6.5 hours. The title compound was purified by column chromatography (5% MeOH in dichloromethane) and was isolated as a 98:2 mixture of isomers (0.040 g, 56.6% yield): ^{1}H NMR (DMSO-d_6) δ 14.4, 14.0 (2s, 1H), 13.4, 13.3 (2s, 1H), 8.7 (m, 1H), 8.1 (m, 2H), 7.8-7.4 (m, 7H); ES-MS (m/z) 322 $[M+1]^+$.

EXAMPLE 199

SYNTHESIS OF 2-(5-(1H-1,2,4-TRIAZOL-5-YL)-1H-INDAZOL-3-YL)BENZO[B]FURAN

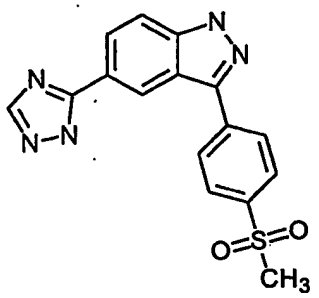


A. 2-(5-(1H-1,2,4-Triazol-5-yl)-1H-indazol-3-yl)benzo[b]furan

The title compound was prepared as described in Example 185 A using 3-benzo[d]furan-2-yl-1H-indazole-5-carboxamide (117 mg, 0.423 mmol). Further purification by prep HPLC afforded the title compound (83 mg, 65% yield): ^{1}H NMR (DMSO-d_6) δ 13.70 (s, 1H), 8.86 (s, 1H), 8.15 (d, 1H), 7.76 (m, 3H), 7.51 (s, 1H), 7.42-7.29 (m, 3H); ES-MS (m/z) 302 $[M+1]^+$.

EXAMPLE 200

SYNTHESIS OF 1-(5-(1H-1,2,4-TRIAZOL-5-YL)(1H-INDAZOL-3-YL))-4-(METHYLSULFONYL)BENZENE



A. 4-Methylthio-1-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazole-3-yl)} benzene

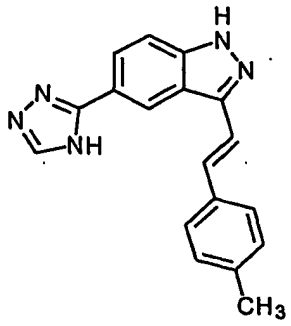
The title compound was prepared as described in Example 194 E using 4-(methylthio)phenylboronic acid (169 mg, 1.01 mmol) (412 mg, 96.0% yield): ES-MS (m/z) 634 $[M+1]^+$.

B. 1-(5-(1H-1,2,4-Triazol-5-yl)(1H-indazol-3-yl))-4-(methylsulfonyl)benzene

A mixture of 4-methylthio-1-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}benzene (200 mg, 0.316 mmol), 1.00 mL CH_2Cl_2, and 3-chloroperoxybenzoic acid (Aldrich, 77% purity, 177 mg, 0.79 mmol based on 77% purity, 2.50 equiv.) was stirred at room temperature for 30 minutes. The reaction was diluted with EtOAc, washed with 2 x sat. aq. $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The crude concentrate was heated in 5.00 mL of MeOH and 5.00 mL of 6.0 N aq. HCl at 65°C for 17.5 h. The mixture was poured onto 6.0 N aq. NaOH and extracted with 2 x EtOAc. The aqueous layer was neutralized to pH = 6.0 with 6.0 N aq. HCl, and extracted with 2 x EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated. Purification by prep HPLC afforded the title compound (10 mg, 9.4% yield): ^1H NMR ($CDCl_3/CD_3OD$) δ 8.82-8.73 (m, 1H), 8.42-8.01 (m, 6H), 7.75-7.65 (m, 1H), 3.18 (s, 3H); ES-MS (m/z) 340 $[M+1]^+$.

EXAMPLE 201

SYNTHESIS OF 3-{3-[(1 E)-2-(4-METHYLPHENYL)VINYL]-1H-INDAZOL-5-YL}-1H-1,2,4-TRIAZOLE



A. 2-{3-[(1E)-2-(4-Methylphenyl)vinyl]-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazoyl} perhydro-2H-pyran

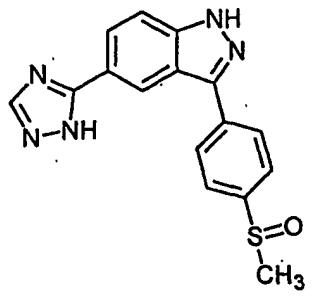
The title compound was prepared according to the procedure described in Example194 using 2-{3-bromo-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran (0.300 g, 0.508 mmol), in ethylene glycol dimethyl ether (5 mL), trans-4-methoxyphenylethenyl boronic acid (0.123 g, 0.762 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.059 g, 0.051 mmol), and potassium phosphate (0.538 g, 2.54 mmol) (0.269 g, 84% yield): ES-MS (m/z) 628 $[M+1]^+$.

B. 3-{3-[(1E)-2-(4-Methylphenyl)vinyl]-1H-indazol-5-yl}-1H-1,2,4-triazole

Hydrolysis was performed by stirring 2-{3-[(1E)-2-(4-methylphenyl)vinyl]-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazoyl}perhydro-2H-pyran (0.269 g, 0.42 mmol) in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl, at room temperature for 6.5 hours. The title compound was purified by column chromatography (5% MeOH in dichloromethane) and isolated as a 97:3 ratio of 2 isomers (0.103g, 81% yield): ^{1}H NMR (DMSO-d_6) δ 8.8 (s, 1H), 8.6 (br s, 1H), 8.1 (d, 1H), 7.6 (m, 3H), 7.5 (d, 2H), 7.0 (d, 2H), 2.34 (s, 3H); ES-MS (m/z) 302 $[M+1]^+$.

EXAMPLE 202

SYNTHESIS OF 1-(5-(1H-1,2,4-TRIAZOL-5-YL)(1H-INDAZOL-3-YL))-4-(METHYLSULFINYL)BENZENE

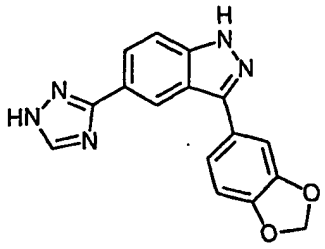


A. 1-(5-(1H-1,2,4-Triazol-5-yl)(1H-indazol-3-yl))-4-(methylsulfinyl)benzene

A mixture of 4-methylthio-1-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}benzene (136 mg, 0.214 mmol), 1.00 mL CH_2Cl_2, and 3-chloroperoxybenzoic acid (Aldrich, 77% purity, 48.1 mg, 0.214 mmol based on 77% purity, 1.00 equiv.) was stirred at room temperature for 30 minutes. The reaction was diluted with EtOAc, washed with 2 x sat. aq. $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The crude concentrate was heated in 5.00 mL of MeOH and 5.00 mL of 6.0 N aq. HCl at 65°C for 17.5 h. The mixture was poured onto 6.0 N aq. NaOH and extracted with 2xEtOAc. The aqueous layer was neutralized to pH = 6.0 with 6.0 N aq. HCl, and extracted with 2xEtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated. Purification by prep HPLC afforded the title compound (7.2 mg, 10.4% yield): ^1H NMR ($CDCl_3/CD_3OD$) δ 8.78 (s, 1H), 8.45-7.98 (m, 4H), 7.86 (d, 2H), 7.72 (d, 1H), 2.89 (s, 3H); ES-MS (m/z) 324 $[M+1]^+$.

EXAMPLE 203

SYNTHESIS OF 5-(5-(1H-1,2,4-TRIAZOL-5-YL)-1H-INDAZOL-3-YL)-2H-BENZO[D] 1,3-DIOXOLENE



A. 5-{1-Perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}-2H-benzo[d]1,3-dioxolene

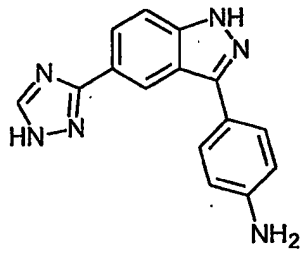
The title compound (168 mg, 52% yield) was prepared as described in Example 194 E using 3,4-(methylenedioxy)phenylboronic acid (134 mg, 0.808 mmol). ES-MS (m/z) 632 $[M+1]^+$.

B. 5-(5-(1H-1,2,4-Triazol-5-yl)-1H-indazol-3-yl)-2H-benzo[d]1,3-dioxolene

The title compound was prepared as described in Example 194 F using 5-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazole-3-yl}-2H-benzo[d]1,3-dioxolene (168 mg, 0.267 mmol). Further purification by HPLC afforded the title compound (7 mg, 9% yield): ^{1}H NMR (DMSO-d_6) δ 13.35 (s, 1H), 8.64 (s, 1H), 8.07 (d, 1H), 7.74-7.37 (m, 4H), 7.13 (d, 1H), 6.12 (s, 2H); ES-MS (m/z) 306 $[M+1]^+$.

EXAMPLE 204

SYNTHESIS OF 4-(5-(1H-1,2,4-TRIAZOL-5-YL)-1H-INDAZOL-3-YL) PHENYLAMINE

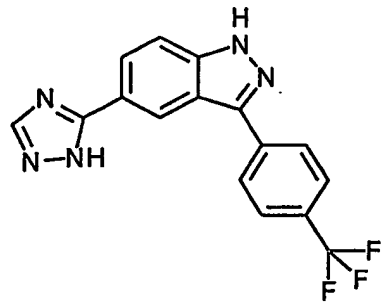


A. 4-(5-(1H-1,2,4-Triazol-5-yl)-1H-indozol-3-yl)phenylamine

The title compound was prepared as described in Example 184 B (40 mg, 28% yield). ^{1}H NMR (DMSO-d_6) δ 14.2 (m, 1H), 13.1 (br s, 1H), 8.60 (br s, 1H), 8.03 (d, 1H), 7.8-7.5 (m, 4H), 6.71 (d, 2H), 5.33 (s, 2H); ES-MS (m/z) 277 $[M+1]^+$.

EXAMPLE 205

SYNTHESIS OF 5-{3-[4-(TRIFLUOROMETHYL)PHENYL]-1H-INDAZOL-5-YL}-1H-1,2,4-TRIAZOLE

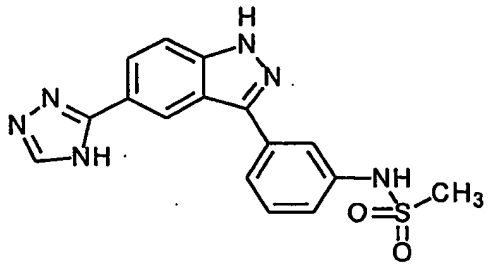


A. 5-{3-[4-(Trifluoromethyl)phenyl]-1H-indazol-5-yl}-1H-1,2,4-triazole

A mixture of 2-{3-bromo-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran (300 mg, 0.508 mmol), 4-trifluoromethylphenylboronic acid (144 mg, 0.758 mmol, 1.49 equiv.), [1,1'-bis(diphenylphosphino)-ferrocene} dichloropalladium (II) complex with dichloromethane (Aldrich), 41.5 mg (0.0508 mmol, 0.100 equiv.), 2.53 mL of anhydrous DME, and powdered potassium phosphate (K_3PO_4, 535 mg, 2.52 mmol, 4.96 equiv.) were refluxed for 5 days. The reaction was diluted with CH_2Cl_2, washed with 2 x sat. aq. $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated. The crude material was purified by silica gel using 30-40% EtOAc in hexanes. To the purified material was added 5.00 mL of MeOH, and 5.00 mL of 6.0 N aq. HCl. The mixture was heated at 60°C for 24 h. The reaction mixture was filtered. The solid was further purified by silica gel chromatography using EtOAc affording the title compound (69.3 mg). Further purification by prep HPLC afforded the title compound (18.9 mg, 11.3% yield): ^{1}H NMR ($CDCl_3/CD_3OD$) δ 8.74 (s, 1H), 8.41-7.97 (m, 4H), 7.78 (d, 2H), 7.66 (d, 1H); ES-MS (m/z) 330 $[M+1]^+$.

EXAMPLE 206

SYNTHESIS OF [3-(5-(1H-1,2,4-TRIAZOL-3-YL)(1H-INDAZOL-3-YL)) PHENYL] (METHYLSULFONYL)AMINE



A. 3-{1-Perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}phenyl amine

To a solution of 2-{3-bromo-5-[1 (triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazolyl}perhydro-2H-pyran (1.0 g, 1.69 mmol) in ethylene glycol dimethyl ether, (20 mL), 3-amino phenyl boronic acid was added as a solid (0.393 g, 2.53 mmol), followed by [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.196 g, 0.169 mmol), and potassium phosphate (1.79 g, 8.45 mmol). The reaction mixture was heated to reflux temperature of the solvent for 12 h. The crude reaction mixture was partitioned between ethyl acetate and water. The organic extracts were dried over Na_2SO_4. The desired product was isolated as a beige solid after column chromatography purification (SiO_2, 25-50% ethyl acetate in hexanes) (0.801 g, 79% yield): ES-MS (m/z) 603 $[M+1]^+$.

B. (Methylsulfonyl)(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenylamine

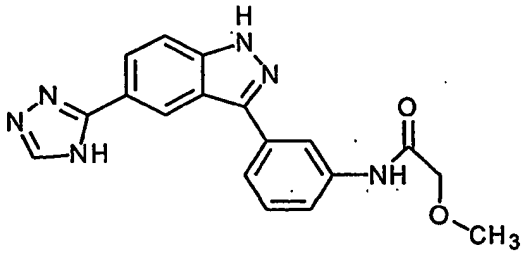
To a solution of 3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}phenylamine (0.125 g, 0.207 mmol), in tetrahydrofuran (5 mL), were added, methane sulfonyl chloride (0.036 g, 0.315 mmol, 0.025 mL) and triethyl amine (0.107 g, 1.06 mmol, 0.147 mL). The reaction mixture was stirred at room temperature for 12 hours. After evaporation of the solvent, the residue was dissolved in 10 mL of ethyl acetate and was washed 3 times with water (5 mL). The crude was used without further purification (0.140 g, 99% yield): ES-MS (mlz) 681 $[M+1]^+$.

C. [3-(5-(1H-1,2,4-Triazol-3-yl)(1H-indazol-3-yl))phenyl](methylsulfonyl)amine

Hydrolysis was performed by stirring (methylsulfonyl)(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)amine (0.140 g, 0.205 mmol) in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl, at room temperature for 18 hours. The title compound was purified by preparative HPLC (15-80% acetonitrile in water) (0.052 g, 71% yield): ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 10.0 (s, 1H), 8.7 (s, 1H), 8.4 (br s, 1H), 8.1 (d, 1H), 7.9 (s, 1H), 7.7 (dd, 2H), 7.5 (dd, 1H), 7.3 (d, 1H), 3.06 (s, 3H); ES-MS (m/z) 355 $[M+1]^+$.

EXAMPLE 207

N-[3-(5-(1H-1,2,4-TRIAZOL-3-YL)(1H-INDAZOL-3-YL))PHENYL]-2-METHOXYACETAMIDE



A. 2-Methoxy-N-(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1 H-indazol-3-yl)}phenyl)acetamide

To a solution of 3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}phenylamine (0.125 g, 0.207 mmol), in tetrahydrofuran (5 mL), were added, 2-methoxy acetyl chloride (0.034 g, 0.315 mmol, 0.025 mL) and triethylamine (0.107 g, 1.06 mmol, 0.147 mL). The reaction mixture was stirred at room temperature for 12 hours. After evaporation of the solvent, the residue was dissolved in 10 mL of ethyl acetate and was washed 3 times with water (5 mL). The crude was used without further purification (0.141g, 99% yield): ES-MS (m/z) 675 $[M+1]^+$.

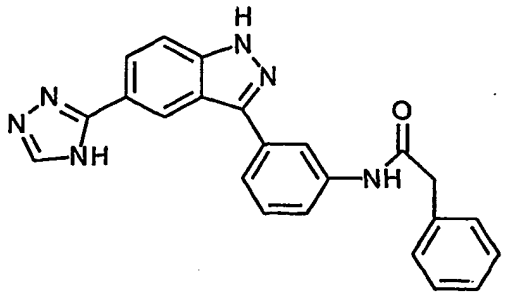
B. N-[3-(5-(1H-1,2,4-Triazol-3-yl)(1H-indazol-3-yl))phenyl]-2-methoxyacetamide

Hydrolysis was performed by stirring 2-methoxy-N-(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)acetamide (0.141 g, 0.207mmol) in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of

6.ON aqueous HCl, at room temperature for 18 hours. The title compound was purified by preparative HPLC (15-80% acetonitrile in water) (0.033 g, 46% yield) ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 10.0 (s, 1H), 8.7 (s, 1H), 8.4 (br s, 1H), 8.3 (s, 1H), 8.1 (d, 1H), 7.8 (d, 1H), 7.7 (d, 2H), 7.5 (dd, 1H), 4.06 (s, 2H), 3.4 (s, 3H); ES-MS (mlz) 349 $[M+1]^+$.

EXAMPLE 208

SYNTHESIS OF N-[3-(5-(1H-1,2,4-TRIAZOL-3-YL)(1H-INDAZOL-3-YL))PHENYL]-2-PHENYLACETAMIDE



A. N-(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)2-phenylacetamide

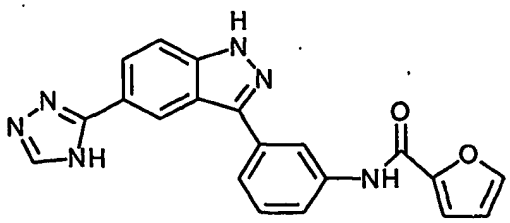
To a solution of 3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}phenylamine (0.125 g, 0.207 mmol), in tetrahydrofuran (5 mL), were added, phenyl acetyl chloride (0.049 g, 0.315 mmol, 0.025 mL) and triethyl amine (0.107 g, 1.06 mmol, 0.147 mL). The reaction mixture was stirred at room temperature for 12 hours. After evaporation of the solvent, the residue was dissolved in 10 mL of ethyl acetate and was washed 3 times with water (5 mL). The crude was used without further purification (0.186 g, 99% yield): ES-MS (m/z) 721 $[M+1]^+$.

B. N-[3-(5-(1H-1,2,4-Triazol-3-yl)(1H-indazol-3-yl))phenyl]-2-phenylacetamide

Hydrolysis was performed by stirring N-(3-{1-perhydro-2H-pyran-2-yl-5-[1 -(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)2-phenylacetamide (0.186 g, 0.207 mmol) in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl, at room temperature for 18 hours. The title compound was purified by preparative HPLC (0.039 g, 48% yield): ^{1}H NMR (DMSO-d_6) δ 13.4 (br s, 1H), 10.4 (s, 1H), 8.7 (s, 1H), 8.4 (br s, 1H), 8.2 (s, 1H), 8.1 (dd, 1H), 7.7-7.6 (m, 3H), 7.5 (t, 1H), 7.4-7.2 (m, 4H); ES-MS (m/z) 395 $[M+1]^+$.

EXAMPLE 209

SYNTHESIS OF N-[3-(5-(1H-1,2,4-TRIAZOL-3-YL)(1H-INDAZOL-3-YL))PHENYL]-2-FURYLCARBOXAMIDE



A. 2-Furyl-N-(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)carboxamide

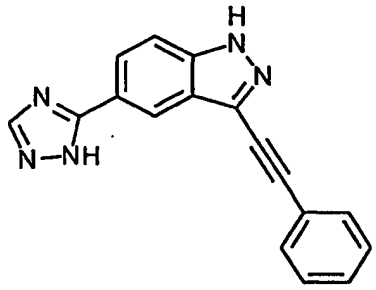
To a solution of 3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}phenylamine (0.125 g, 0.207 mmol), in tetrahydrofuran (5 mL), were added, 2-furoyl chloride (0.041 g, 0.315 mmol, 0.031 mL) and triethyl amine (0.107 g, 1.06 mmol, 0.147 mL). The reaction mixture was stirred at room temperature for 12 hours. After evaporation of the solvent, the residue was dissolved in 10 mL of ethyl acetate and was washed 3 times with water (5 mL). The crude was used without further purification (0.150 g, 99% yield): ES-MS (m/z) 697 $[M+1]^+$.

B. N-[3-(5-(1H-1,2,4-Triazol-3-yl)(1H-indazol-3-yl))phenyl]-2-furylcarboxamide

Hydrolysis was performed by stirring 2-furyl-N-(3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)carboxamide (0.150 g, 0.207 mmol) in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl, at room temperature for 18 hours. The title compound was purified by preparative HPLC (15-80% acetonitrile in water) (0.050 g, 50% yield): ^{1}H NMR (DMSO-d_6) δ 8.8 (s, 1H), 8.6 (s, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 7.8-7.7 (m, 4H), 7.5 (t, 1H), 7.3 (d, IH), 6.6 (m, 1H); ES-MS (m/z) 371 $[M+1]^+$.

EXAMPLE 210

SYNTHESIS OF 5-[3-(2-PHENYLETHYNYL)-1H-INDAZOL-5-YL]-1H-1,2,4-TRIAZOLE

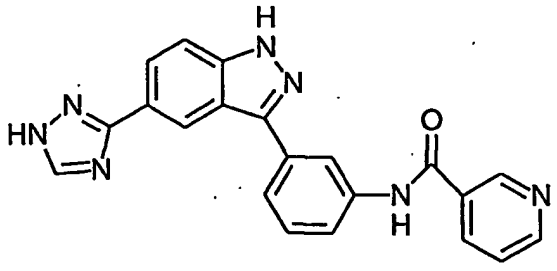


A. 5-[3-(2-phenylethynyl)-1H-indazol-5-yl]-1H-1,2,4-triazole

The title compound was prepared as described in Example 185 A using 3-(2-phenylethynyl)-1H-indazole-5-carboxamide (73.8 mg, 0.282 mmol). Further purification by prep HPLC afforded the title compound (11.7 mg, 14.6% yield): ^{1}H NMR (DMSO-d_6) δ 13.71 (br, 1H), 8.46 (s, and br s, 2H), 8.12 (d, 1H), 7.78-7.65 (in, 3H), 7.51-7.47 (m, 3H); ES-MS (m/z) 286 $[M+1]^+$.

EXAMPLE 211

SYNTHESIS OF N-[3-(5-(1H-1,2,4-TRIAZOL-3-YL)(1H-INDAZOL-3-YL))PHENYL]-3-PYRIDYLCARBOXAMIDE



A. N-[3-{1-Perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)-3-pyridylcarboxamide

To a solution of 3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)]-1H-indazol-3-yl}phenylamine (0.250 g, 0.415 mmol), in tetrahydrofuran (5

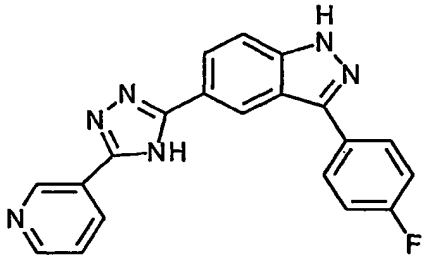
mL), were added, nicotinoyl chloride-hydrochloride (0.148 g, 0.83 mmol), triethyl amine (0.210 g, 2.07 mmol, 0.289 mL), and 2 mL of dimethyl formamide. The reaction mixture was stirred at room temperature for 12 hours. After evaporation of the solvent, the residue was dissolved in 10 mL of ethyl acetate and was washed 3 times with water (5 mL). The crude was used without further purification. ES-MS (m/z) 708 $[M+1]^+$.

B. N-[3-(5-(1H-1,2,4-Triazol-3-yl)(1H-indazol-3-yl))phenyl]-3-pyridylcarboxamide

Hydrolysis was performed by stirring N-[3-{1-perhydro-2H-pyran-2-yl-5-[1-(triphenylmethyl)(1,2,4-triazol-3-yl)](1H-indazol-3-yl)}phenyl)-3-pyridylcarboxamide in 4 mL of 4.0 N commercial solution of HCl in dioxane and 2 mL of 6.0 N aqueous HCl, at room temperature for 18 hours. The title compound was purified by preparative HPLC and neutralized with aqueous sodium hydroxide (0.046 g, 29 % yield over 2 steps): ^{1}H NMR (DMSO-d_6) δ 8.8 (s, 1H), 8.6 (s, 1H), 8.3 (s, 1H), 8.0 (d, 1H), 7.8-7.7 (m, 4H), 7.5 (t, 1H), 7.3 (d, 1H), 6.6 (m, 1H); ES-MS (m/z) 382 $[M+1]^+$.

EXAMPLE 212

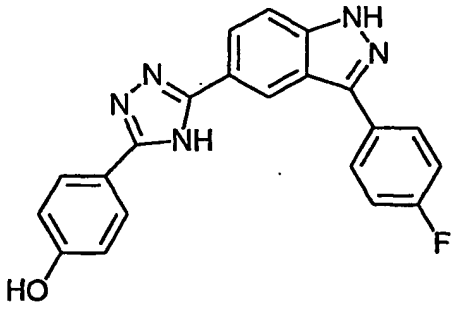
SYNTHESIS OF 5-[3-(4-FLUOROPHENYL)(1H-INDAZOL-5-YL)]-3-(3-PYRIDYL)-4H- 1,2,4-TRIAZOLE



The procedure described in Example 123 using ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methylanimine hydrochloride (200 mg, 0.62 mmol), triethylamine (0.25ml, 1.86 mmol), and nicotinic hydrazide (171.4 mg, 1.25 mmol) was used to prepare the title compound (124 mg, 56% yield). ^{1}H NMR (DMSO-d_6) δ 9.45 (s, 1H), 9.05 (d, 1H), 8.8 (m, 2H), 8.18 (d, 1H), 8.0-8.1 (m, 3H), 7.75 (d, 1H), 7.33 (t, 2H), ES-MS m/z 357 $[M+H]^+$.

EXAMPLE 213

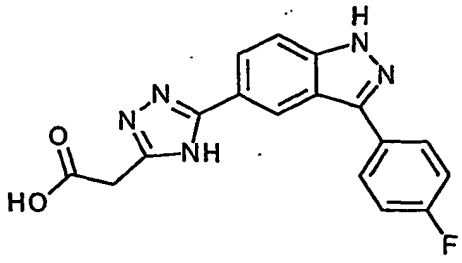
SYNTHESIS OF 4-{5-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]-4H-1,2,4-TRIAZOL-3-YL} PHENOL



To a round bottom flask containing 1-{5-[3-(4-fluorophenyl)(1H-indazol-5-yl)](4H-1,2,4-triazol-3-yl)]-4-methoxybenzene (100 mg, 0.26 mmol) was added anhydrous dichloromethane (2 ml). The flask, under a nitrogen atmosphere, was placed in an ice/salt bath. To the flask was added boron tribromide (1.3 ml, 1.3 mmol). The reaction was allowed to stir at 0^0C for one hour and at room temperature for an additional four hours. The reaction was quenched with water and the solvent was removed. The product was extracted from the reaction mixture with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered and concentrated . The product was purified by semipreparative HPLC (20-80 % acetonitrile over 30 minutes) to yield the title compound (18 mg, 18.7% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 9.95 (s, 1H), 8.65 (s, 1H), 8.1 (m, 3H), 7.95 (m, 2H), 7.78 (d, 1H), 7.4 (m, 2H), 6.85 (m, 2H), ES-MS m/z 372 $[M+H]^+$.

EXAMPLE 214

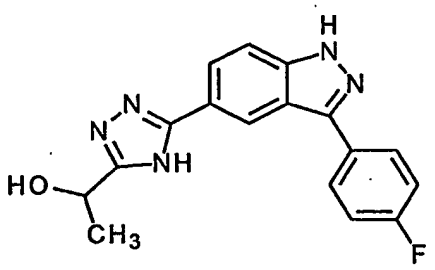
SYNTHESIS OF 2-{5-[3-(4-FLUOROPHENYL)1H-INDAZOL-5-YL]-4H-1,2,4-TRIAZOL-3-YL}ACETIC ACID



To a round bottom flask containing ethyl 2-{5-[-(4-fluorophenyl)-1H-indazol-5-yl]-4H-1,2,4-triazol-3-yl}acetate (100 mg, 0.27 mmol) was added ethanol (1.5 ml), and the compound was dissolved in the solvent. To the flask was added 10% NaOH solution, and the reaction was allowed to stir for three hours. The compound was soluble in the aqueous layer so the solvent was removed. The compound was taken up in methanol and the solution was filtered. The organic layer was concentrated and the product was purified by semipreparative HPLC (20-80 % acetonitrile over 30 minutes) to yield the title compound (24 mg, 26 % yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.6 (s, 1H), 8.0-8.1 (in, 3H), 7.66 (d, 1H), 7.42 (m, 2H), 2.6 (s, 2H), ES-MS m/z 338 $[M+H]^+$.

EXAMPLE 215

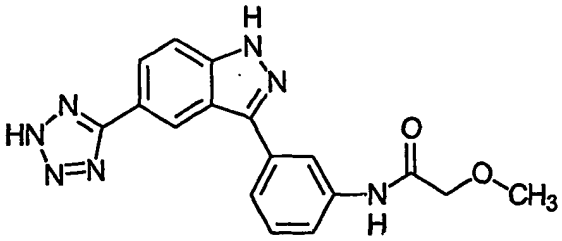
SYNTHESIS OF 1-{5-{3-(4-FLUOROPHENYL)1H-INDAZOL-5-YL}-4H-1,2,4-TRIAZOL-3-YL}ETHAN-1-OL



To a round bottom flask was added ethanol (12 ml), hydrazine monohydrate (0.61 ml, 0.0127 mol), and methyl lactate (1.8 ml, 0.019 mol). This was allowed to heat at 60°C for three hours, then to 75°C for three hours, and left to stir at room temperature overnight. Solvent and excess methyl lactate were removed under reduced pressure and the reaction mixture was diluted with additional ethanol. To the flask was bubbled in gaseous hydrochloric acid, a solid formed in solution. This was collected by filtration and washed with ethanol to yield N-amino-2-hydroxypropanamide. To a round bottom flask was added ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methylanimine hydrochloride (200 mg, 0.62 mmol), triethylamine (0.25 mL, 1.86 mmol), and N-amino-2-hydroxypropanamide (150 mg, 1.25 mmol). This was taken up in anhydrous ethanol (10 mL) and sodium sulfate was added to the reaction mixture. The reaction was allowed to stir at 75°C overnight while under a nitrogen atmosphere. The solvent was removed and the material was purified by semipreparative HPLC (20-80 % acetonitrile over 30 minutes) to yield the title compound (30 mg, 15 % yield). ^{1}H NMR (DMSO-d_6) δ 13.4 (s, 1H), 8.6 (s, 1H), 8.0-8.1 (m, 3H), 7.65 (d, 1H), 7.4 (t, 2H), 4.9 (m, lH), 1.5 (d, 3H), ES-MS m/z 324 $[M+H]^+$.

EXAMPLE 216

SYNTHESIS OF N-[3-(5-(2H-1,2,3,4-TETRAZOL-5-YL)(1H-INDAZOL-3-YL))PHENYL]-2-METHOXYACETAMIDE



A. 2-(5-(2H-1,2,3,4-Tetrazol-5-yl)-3-bromo-1H-indazolyl)perhydro-2H-pyran

To a solution of 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (1.0 g, 3.27 mmol), in toluene (30 mL), was added tributyltin (2.270 mL, 8.2 mmol). The reaction mixture was heated to reflux temperature of the solvent for 8 hours. Volatile materials were removed under reduced pressure. The oily residue was dissolved in 20 mL of toluene and hydrogen chloride gas was bubbled through the solution for 20 min resulting in the formation of a suspension. The pH of the reaction was adjusted to 5 and the product was extracted with ethyl acetate (0.560 g, 48.5 % yield): ES-MS (m/z) 350 $[M+H]^+$.

B. 2-{3-Bromo-5-[2-(triphenylmethyl)(1,2,3,4-tetrazol-5-yl)]-1H-indazolyl}perhydro-2H-pyran

To a solution of 2-(5-(2H-1,2,3,4-tetrazol-5-yl)-3-bromo-1H-indazolyl)perhydro-2H-pyran (0.554 g, 1.59 mmol) in dimethyl formamide (5 mL) was added triphenylmethyl chloride (0.662 g, 2.38 mmol), and triethyl amine (1.110 mL, 7.95 mmol). The reaction was heated to reflux temperature for 3.5 hours and maintained at room temperature overnight. The solvent was removed under reduced pressure. The resulting solid was dissolved in 20 mL of ethyl acetate and was washed with 10 ml-portions of water. The title compound was purified by column chromatography (SiO_2, 20% ethyl acetate in hexanes) (0.754 g, 70%): ES-MS (m/z) mass not detected.

C. 3-{1-Perhydro-2H-pyran-2-yl-5-[2-(triphenylinethyl)(1,2,3,4-tetrazol-5-yl)]-1H-indazol-3-yl}phenylamine

The title compound was prepared according to the procedure described in example 209A using 2-{3-bromo-5-[2-(triphenylmethyl)(1,2,3,4-tetrazol-5-yl)]-1H-

indazolyl}perhydro-2H-pyran (0.754 g, 1.27 mmol) in ethylene glycol dimethyl ether (12 mL), 3-aminophenyl boronic acid (0.296 g, 1.91 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.147 g, 0.127 mmol), and potassium phosphate (1.35 g, 6.35 mmol). It was isolated after chromatographic purification using 25% ethyl acetate in hexanes (0.246g, 32% yield): ES-MS (m/z) 604 $[M+H]^+$.

D. 2-Methoxy-N-(3-{1-perhydro-2H-pyran-2-yl-5-[2-(triphenylmethyl)(1,2,3,4-tetrazol-5-yl)](1H-indazol-3-yl)}phenyl)acetamide

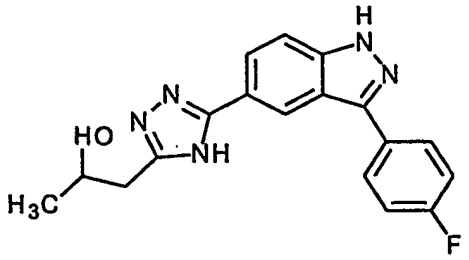
To a solution of 3-{1-perhydro-2H-pyran-2-yl-5-[2-(triphenylmethyl)(1,2,3,4-tetrazol-5-yl)]-1H-indazol-3-yl}phenylamine (0.246 g, 0.407 mmol) in tetrahydrofuran (4 mL) was added 2-methoxyacetyl chloride (0.056 mL, 0.61 mmol) and triethyl amine (0.284 mL, 2.035 mmol). The reaction mixture was stirred overnight at room temperature before being partitioned between ethyl acetate and water. The product was purified by column chromatography (40% ethyl acetate in hexanes) (0.104 g, 38% yield): ES-MS (m/z) M+ was not detected.

E. N-[3-(5-(2H-1,2,3,4-Tetrazol-5-yl)(1H-indazol-3-yl))phenyl]-2-methoxyacetamide

2-Methoxy-N-(3-{1-perhydro-2H-pyran-2-yl-5-[2-(triphenylinethyl)(1,2,3,4-tetrazol-5-yl)](1H-indazol-3-yl)}phenyl)acetamide was dissolved in 3 mL of 4.0 N hydrogen chloride solution in dioxane. Aqueous hydrogen chloride solution (1.0 mL, 6.0 N) was added and the solution was stirred at room temperature for 48 hours. The pH of the reaction mixture was made basic using 2.0 N aqueous sodium hydroxide and organic impurities were extracted with ethyl acetate. The pH of the aqueous phase was then adjusted to 4-5 using aqueous hydrochloric acid and the crude compound was extracted with ethyl acetate. The title compound was purified by preparative HPLC (15-80% acetonitrile in water) (0.025 g, 48% yield): ^{1}H NMR (DMSO-d_6) δ 13.6 (s, 1H), 9.9 (s, 1H), 8.8 (s, 1H), 8.4 (s, 1H), 8.07 (d, 1H), 7.82 (d, 1H), 7.74 (d, 1H), 7.5 (t, 1H), 5.7 (s, 2H), 4.4 (s, 3H); ES-MS (m/z) 350 $[M+H]^+$.

EXAMPLE 217

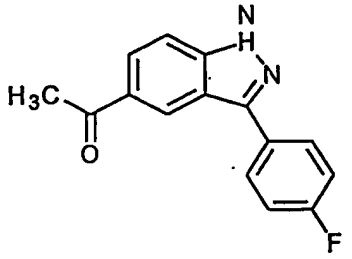
SYNTHESIS OF 1-{5-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL}-4H-1,2,4-TRIAZOL-3-YL}PROPAN-2-OL



To a flask was added ethyl-3-hydroxybutyrate (2.46 mL, 0.019 mmol), hydrazine monohydrate (0.61 mL, 0.0127 mmol) and ethanol (12 mL). This was allowed to stir under a nitrogen atmosphere at 75°C overnight. Gaseous hydrochloric acid was bubbled into the reaction and a solid crashed out of solution that was collected by filtration. This compound was determined to be N-amino-3-hydroxybutanamide. To a round bottom flask was added ethoxy[3-(4-fluorophenyl)(1H-indazol-5-yl)]methylanimine hydrochloride (200 mg, 0.62 mmol), triethylamine (0.25 mL, 1.86 mmol), and N-amino-3-hydroxybutanamide (175 mg, 1.25 mmol). This was taken up in anhydrous ethanol (10 mL) and sodium sulfate was added to the reaction mixture. The reaction was allowed to stir at 75°C overnight while under a nitrogen atmosphere. The solvent was removed and the material was purified by semipreparative HPLC (20-80 % acetonitrile over 30 minutes) to yield the title compound (60 mg, 28% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (s, 1H), 8.6 (s, 1H), 8.05 (m, 3H), 7.7 (d, 1H), 7.4 (t, 2H), 4.1 (m, 1H), 2.85 (d, 2H), 1.15 (d, 3H); ES-MS m/z 338 $[M+H]^+$.

EXAMPLE 218

SYNTHESIS OF 1-[3-(4-FLUOROPHENYL)-1H-INDAZOL-5-YL]ETHAN-1-ONE



A. 1-[3-(4-Fluorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazol-5-yl]ethan-1-one

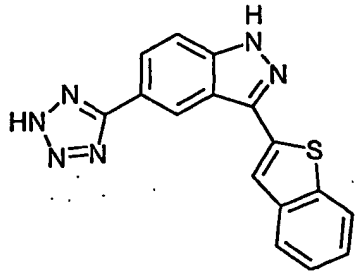
To a solution of 3-(4-fluorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole--5-carbonitrile (215 mg, 0.67 mmol) in THF (10 mL) at -78°C was added methyl lithium (1.0 mL of a 1.0 molar solution, 1.0 mmol). The reaction was allowed to warm to room temperature over 3 hours when it was quenched with water (80 mL) and extracted with ethyl acetate (3x30 mL). The combined ethyl acetate layers were dried (Na_2SO_4) and concentrated to an oil. The product was recovered from the crude by chromatography on silica gel eluting with 20% ethyl acetate/hexane to give 100 mg of a white solid (44% yield). ES-MS (m/z) 339 $[M+1]^+$.

B. 1-[3-(4-fluorophenyl)-1H-indazol-5-yl]ethan-1-one

To a solution of 1-[3-(4-fluorophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazol-5-yl]ethan-1-one (100 mg, 0.30 mmol) in methanol (30 mL) was added 6N HCl (30 mL). The solution was stirred at room temperature for 4.5 hours when the methanol was removed under vacuo and the solution made basic with saturated Na_2CO_3. The suspension was then filtered and the product dried to give the title compound (83 mg, 100% yield). ^1H NMR (DMSO-d_6) δ 8.64 (s, 1H), 8.1 (m, 2H), 7.97 (d, 1H), 7.67 (d, 1H), 7.40 (t, 2H), 2.69 20 (s, 3H); ES-MS (m/z) 255 $[M+1]^+$.

EXAMPLE 219

SYNTHESIS OF 2-(5-(1H-1,2,3,4-TETRAAZOL-5-YL)-1H-INDAZOL-3-YL)BENZO[B]THIOPHENE

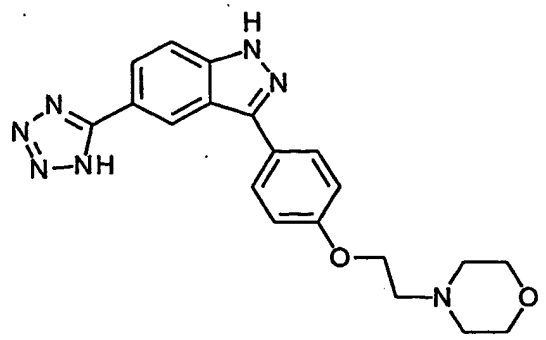


A. 2-(5-(1H-1,2,3,4-Tetraazol-5-yl)-1H-indazol-3-yl)benzo[b]thiophene

The title compound was prepared as described in Example 170.A using 3-benzo[b]thiophen-2-yl-1H-indazole-5-carbonitrile (294 mg, 1.07 mmol) (19.5 mg, 5.7 % yield): ^1H NMR (DMSO-d_6) δ 13.72 (s, 1H), 8.95 (s, 1H), 8.21 (s, 1H), 8.13 (d, 1H), 8.03(d, 1H), 7.98 (d, 1H), 7.86 (d, 1H), 7.48-7.39 (m, 2H); ES-MS (m/z) 319 $[M+1]^+$.

EXAMPLE 220

SYNTHESIS OF 1-(5-(1H-1,2,3,4-TETRAAZOL-5-YL)(1H-INDAZOL-3-YL))-4-(2-MORPHOLIN-4-YLETHOXY)BENZENE



A. 3-[4-(2-Morpholin-4-yl-ethoxy)phenyl]-1H-indazole-5-carbonitrile

A mixture of 3-(4-hydroxyphenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (400 mg, 1.25 mmol), triphenylphosphine (Ph_3P, 1.31 g, 5.00 mmol, 4.00 equiv.), 4.00 mL THF, 4-(2-hydroxyethyl)morpholine (656 mg, 5.00 mmol, 4.00 equiv.), and diethyl azodicarboxylate (DEAD, 871 mg, 5.00 mmol, 4.00 equiv.) were stirred at room temperature for 5 days. The reaction was diluted with EtOAc and washed with 2 x 6.0 N aq. HCl. The combined aqueous layers were extracted with 2 x EtOAc. The acidic aqueous layer was allowed to stand at room temperature for 5 h, and then added to enough 6.0 N aq. NaOH such that the final pH > 12.0. The aqueous layer was extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated. Purification by silica gel chromatography using 0-5% MeOH in EtOAc as eluent afforded an oil. Sonication of the oil in 15 mL of 10% EtOAc/hexane gave a precipitate. This mixture was diluted with 18 mL of hexanes, sonicated, and filtered affording the title compound (310 mg, 71.1% yield: ES-MS (m/z) 349 $[M+1]^+$.

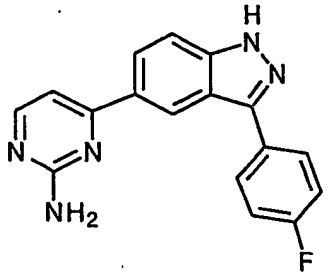
B. 1-(5-(1H-1,2,3,4-Tetraazol-5-yl)(1H-indazol-3-yl))-4-(2-morpholin-4-ylethoxy)benzene

A mixture of 3-[4-(2-morpholin-4-ylethoxy)phenyl]-1H-indazole-5-carbonitrile (290 mg, 0.832 mmol), azidotributyltin (Bu_3SnN_3, 1.56 g, 4.70 mmol, 5.65 equiv.), and 9.0 mL toluene was refluxed for 17.5 h and concentrated to an oil. To the oil was added 6.5 mL of dioxane and 6.5 mL of 6.0 N aq. HCl. The mixture was stirred at room temperature for 4 h and then added to 25 mL of 6.0 N aq. NaOH. The mixture was

extracted with 3 x hexanes, and 3 x Et_2O. The aqueous layer was filtered to remove particulates. The pH was adjusted with 6.0 N aq. HCl to give maximum visual turbidity (approximately pH 5.0 - 5.5) and then the mixture was extracted with 2 x EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated. The product was triturated in 5% EtOAc in hexanes. Filtration and drying of the solid afforded the title compound (29.0 mg, 8.90% yield): ^{1}H NMR ($CDCl_3/CD_3OD$) δ 8.75 (s, 1H), 8.08 (d, 1H), 7.95 (d, 2H), 7.70 (m, 1H), 7.13 (d, 2H), 4.30 (t, 2H), 3.85-3.79 (m, 4H), 3.07 (t, 2H), 2.89-2.80 (m, 4H); ES-MS (m/z) 392 $[M+1]^+$.

EXAMPLE 221

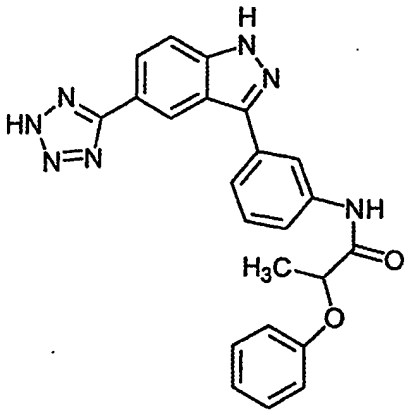
SYNTHESIS OF 4-[3-(4-FLUOROPHENYL)-1H-INDAZOLE-5-YL]PYRIMIDINE-2-YLAMINE



A solution of 1-[3-(4-fluorophenyl)-1H-indazol-5-yl]ethan-1-one (73 mg, 0.29 mmol) in dimethoxy DMF acetal (25 mL) was heated to 90°C overnight. The solution was then concentrated to an oil under vacuo when methanol (10 mL), guanidine (55 mg, 0.57 mmol), and NaOMe (290 µL of a 2 N solution, 0.58 mmol) was added. The reaction was then heated in a sealed tube to 120°C overnight. The reaction was then acidified with trifluoroacetic acid then subjected to preparative HPLC (CH_3CN/water 0.1%TFA) to recover the final compound (3 mg, 3% yield). ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 8.78 (s, 1H), 8.35 (d, 1H), 8.19 (d, 1H), 8.06 (dd, 2H), 7.72 (d, 1H), 7.53 (d, 1H), 7.38 (t, 2H); ES-MS (m/z) 306 $[M+1]^+$.

EXAMPLE 222

SYNTHESIS OF N-[3-(5-2H-1,2,3,4-TETRAZOL-5-YL)(1H-INDAZOL-3-YL))PHENYL]2-PHENOXYPROPANAMIDE



A. 3-(3-aminophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile

The title compound was prepared as described in example 161 using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (1.7 g, 5.55 mmol), in ethylene glycol dimethyl ether (60 mL), 3-amino boronic acid (1.72 g, 11.10 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.641 g, 0.555 mmol), and potassium phosphate (5.89 g, 27.75 mmol). A second batch was prepared using 3-bromo-1-perhydro-2H-pyran-2-yl-1H-indazole-5-carbonitrile (2.0 g, 6.53 mmol), in ethylene glycol dimethyl ether (70 mL), 3-amino boronic acid (2.025 g, 13.06 mmol), [1,1'-bis(diphenylphosphino)-ferrocene] complex with dichloromethane (1:1) (0.755 g, 0.653 mmol), and potassium phosphate (6.92 g, 32.65 mmol). The crude compounds were combined and purified by column chromatography using 30% ethyl acetate in hexanes (3.2 g, 82 % yield): ES-MS (m/z) 319 $[M+H]^+$.

B. N-[3-(5-Cyano-1-perhydro-2H-pyran-2-yl-(1H-indazole-3-yl))phenyl]-2-phenoxypropanamide

To a solution of 3-(3-aminophenyl)-1-perhydro-2H-pyran-2-yl-1H-indazole--5-carbonitrile (0.300 g, 0.94 mmol) in dichloromethane (10 mL) was added 2-phenoxy propionic acid (0.172 g, 1.034 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.216 g, 1.13 mmol). After overnight reaction at room temperature, the reaction mixture was partitioned between dichloromethane and water. The organic phase